Definition and Application of Terms for Vaccine Pharmacovigilance

Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance

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Working Group on Vaccine Pharmacovigilance

CIOMS

World Health Organization

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ISBN 978 92 9036 083 4

The authors alone are responsible for the views expressed in this publication and those views do not necessarily represent the decisions, policies or views of their respective institutions or companies.

Acknowledgements

The Council for International Organizations of Medical Sciences (CIOMS) with the World Health Organization (WHO) gratefully acknowledges the contributions of the members of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance as well as the drug and vaccine regulatory authorities, vaccine industry, and other organizations and institutions which by providing these experts and resources supported the work that resulted in this publication. The work has required a number of meetings organized by the CIOMS Secretariat in collaboration with WHO. The consistent contribution of WHO was represented particularly by its Department of Immunization, Vaccines and Biologicals and its Department of Essential Medicines and Pharmaceutical Policies. Dr Philippe Duclos of the WHO Department of Immunization, Vaccines and Biologicals was instrumental in the establishment of this joint CIOMS/WHO Working Group in 2004-2005, supported by Drs Mary Couper and Shanthi Pal of the Department of Essential Medicines and Pharmaceutical Policies, as well as Professor Ulrich Heininger and Dr Elizabeth Loupi as representatives of the Brighton Collaboration. Moreover, contributions from regulatory agencies and vaccine manufacturers that hosted the meetings (see Annex 1) are especially acknowledged.

During this process helpful discussions were held with concerned parties such as the Brighton Collaboration, the US Centers for Disease Control and Prevention (CDC), the Public Health Agency of Canada and the Maintenance and Support Services Organization (MSSO) of the Medical Dictionary for Regulatory Activities (MedDRA). A number of parties, including relevant regulators in the European Union via the Committee for Medicinal Products (CHMP) Pharmacovigilance Working Party (PhVWP) at the European Medicines Agency, the Global Advisory Committee on Vaccine Safety of WHO and selected individual vaccine safety experts, were consulted on the general definitions for adverse events following immunization (AEFIs). Each Working

Group member participated actively in the discussions, drafting and redrafting of texts and their review, which enabled the Working Group to bring the entire project to a successful finalization. During the process new members were invited in capacity of their expertise.

CIOMS thanks especially those members who chaired the meetings of the Working Group for their dedication and capable leadership. Each of the meetings had a nominated rapporteur (or rapporteurs), and CIOMS acknowledges their professional contributions.

The Editorial Group, comprising Drs Adwoa D Bentsi-Enchill, Priya Bahri, Michael D Blum, Ulrich Heininger, and Eliane Matos dos Santos, merits special mention and thanks. At WHO, Drs Duclos, Bentsi-Enchill and Patrick Zuber have supported the management of the Working Group. CIOMS wishes to express special appreciation to Dr Bentsi-Enchill who, as Chief Editor of the final report, assured the quality of the publication.

CIOMS and the Working Group are grateful for important input received on several points of the report from many senior experts outside the Group who reviewed the entire manuscript and made valuable suggestions.

At CIOMS, Dr Juhana E Idänpään-Heikkilä, former Secretary-General, Dr Gottfried Kreutz, former Secretary-General, Dr Gunilla Sjölin-Forsberg, Secretary-General and Ms Amanda Owden, Administrative Assistant managed the project. Mr Sev Fluss contributed with editorial work and Ms Owden and Ms Louise Wakeford provided secretarial support throughout the project.

Geneva, June 2011

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Abbreviations and glossary

ADR	adverse drug reaction
AEFI	adverse event following immunization
AERS	US Adverse Event Reporting System (for drugs other than vaccines – see also VAERS below)
ANVISA	Agência Nacional de Vigilância Sanitária (Brazilian Health Surveillance Agency)
BCG	Bacillus Calmette-Guérin (vaccine)
CDC	US Centers for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
DCVMN	Developing Countries Vaccine Manufacturers Network
DTP	diphtheria-tetanus-pertussis (vaccine)
EEG	electroencephalography/electroencephalogram
EV	eczema vaccinatum
GBS	Guillain-Barré syndrome
GV	generalized vaccinia
HHE	hypotonic-hyporesponsive episode
HLT	High Level Term (in MedDRA)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
LLT	Lower Level Term (in MedDRA)
MedDRA	Medical Dictionary for Regulatory Activities
MMR	measles-mumps-rubella (vaccine)
MRI	magnetic resonance imaging

MSSO	Maintenance and Support Service Organization (for MedDRA)
OPV	oral polio vaccine
PSUR	Periodic safety update repots
PT	Preferred Term (in MedDRA)
PV	progressive vaccinia
SIDS	sudden infant death syndrome
SMQ	Standardized MedDRA Queries
UMC	Uppsala Monitoring Centre (the WHO Collaborating Centre for International Drug Monitoring)
VAERS	US Vaccine Adverse Event Reporting System (see also AERS above)
WBC	white blood cells
WHO	World Health Organization
WHO-ART	WHO Adverse Reaction Terminology

Glossary and explanatory notes

The following explanatory notes are also provided as footnotes in relevant sections of the text where appropriate (e.g., on first use of the related term):

Drugs versus medicinal products

The term "drugs" has been used where there is a comparison between or reference to "vaccines" versus "drugs", whereas "medicinal products" is used where the intention (i.e. meaning of the relevant text) is to cover vaccines and drugs in one term.

Immunization and vaccination

"Immunization" as used in this report means the usage of a vaccine for the purpose of immunizing individuals. "Usage" includes all processes that occur after a vaccine product has left the manufacturing/packaging site, i.e. handling, prescribing and administration of the vaccine.

It is generally acknowledged that (1) "immunization" is a broader term than "vaccination", including active and passive immunization, and (2) immunization when used strictly implies an immune response. In keeping with other key published literature in the field of immunization, the terms "immunization" and "vaccination" are – in general – used interchangeably in the current report. For consistency, a few specific phrases where either term was considered to be implicit or in common use have been maintained (e.g., "immunization programme", "mass vaccination campaign").

Signal

Information that arises from one or multiple sources (including observations and experiments) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action. [*Practical aspects of signal detection in pharmacovigilance.* Report of CIOMS Working Group VIII. Geneva, CIOMS, 2010.]

Vaccine approval, authorization or licensure

The terms "approval", "authorization" and "licensure" in the context of vaccine (and drug) regulation in different jurisdictions mean the declaration by a regulatory authority that a product following review was found to have a positive risk/benefit and the product is approved for marketing and use. For consistency, we have adopted "licensure" to cover any of these regulatory procedures or declarations. "Marketing" (or "post-marketing", etc.) is usually used to describe the phase of vaccine distribution following the manufacturer's decision to market the vaccine. The manufacturer may decide not to market a product even though licensure has been granted by the regulatory authority. While "marketing" differs in meaning we have adopted, for consistency, the term "post-licensure" throughout this report to include everything that follows licensing of the product (i.e., "post-licensure" includes post-marketing considerations that would apply in the specific context in which the term is used).

Vaccine lot, vaccine batch

Different jurisdictions use the terms "vaccine lot" and "vaccine batch" differently; in this report they are used interchangeably.

Vaccine quality defect

For the purpose of this report, a "vaccine quality defect" is defined as any deviation of the vaccine product as manufactured from its set quality specifications.

Foreword

The CIOMS/WHO Working Group on Vaccine Pharmacovigilance was initiated in 2005 with the vision to globally support surveillance of vaccine safety and the evolving need of a harmonized view on terminology and case definitions used in vaccine pharmacovigilance. Specifically, the group was to provide tools for higher excellence of signal detection and investigation of adverse events following immunization (AEFIs), and to contribute to the development and dissemination of definitions of AEFIs as developed by the Brighton Collaboration process (https://brightoncollaboration.org/public).

This publication is jointly supported by CIOMS and WHO and can be regarded as a specific contribution to a series of CIOMS Working Groups on Drug Safety, in this particular case Vaccine Safety. Previous working groups have established the CIOMS reporting form for cases of adverse reactions, set standards for periodic safety update reports (PSURs), developed proposals for harmonized safety information of data sheets or package inserts, presented approaches for assessing benefit-risk, discussed aspects of day-to-day pharmacovigilance work affecting management and interpretation of safety data, management of safety information in clinical trials and standards for the development of safety update reports. Recently, the practical aspects of signal detection were published.

The rationale for a joint initiative with WHO was easy to see considering the specific role of WHO in relation to global recommendations and policies for immunization programmes.

A system of international pharmacovigilance needs to have information exchange and communication about vaccine safety using common terminology that is user-friendly and not too complicated but still has necessary precision. With this purpose, CIOMS has previously (1999) published defined terms and criteria for reporting adverse drug reactions, including those for vaccines (see Annex 2 for a list of selected CIOMS publications relevant to pharmacovigilance).

The increasing need of additional agreed adverse drug reaction terms and definitions for vaccine pharmacovigilance such as those developed by the Brighton Collaboration was identified as part of the rationale to launch this Working Group. Growing attention to vaccine safety and the potential

impact of AEFIs, as well as experiences from mass vaccination campaigns during the last years and recently of the global influenza A/H1N1 pandemic, have verified this need. Large exposures of a population to a vaccine such as the pandemic influenza vaccine over a short time period and high numbers of reports on suspected AEFIs have stressed the need of definitions with higher specificity and selectivity supporting case detection, expedited handling, analyses and signal detection work in monitoring vaccine safety.

The CIOMS/WHO Working Group on Vaccine Pharmacovigilance was to: (1) Develop general definitions focused on vaccine pharmacovigilance; (2) Contribute to the development, review, evaluation and approval of AEFI case definitions developed by the Brighton Collaboration process and to their dissemination; and (3) Collaborate with other CIOMS Working Groups especially that on Standardized MedDRA Queries (SMQs) and CIOMS VIII on signal detection.

In order to fulfil the second objective, the Working Group agreed to endorse already existing Brighton Collaboration case definitions, participate in the review of case definitions under development, propose priorities for the development of new case definitions and facilitate translation and dissemination of the case definitions.

In relation with the third objective, the Working Group has contributed with an evaluation of the comparability between SMQs and Brighton Collaboration case definitions and provided vaccine expertise to support the work and published document of the CIOMS Working Group VIII on *Practical Aspects of Signal Detection in Pharmacovigilance*.

Following these experiences, the Working Group is pleased to publish this document reflecting its efforts and conclusions. This publication is a product of the compiled joint work of all parties represented and the target audience is health-care professionals concerned with vaccination within academia, regulatory and public health agencies, and the vaccine industry globally. It is based on several consecutive meetings of the Working Group convened by CIOMS over the last five years (2005-2010). The discussions of experts within the Working Group and consultations with other experts have resulted in agreement on case definitions and selected terminology for AEFIs and on their use in vaccine safety surveillance and international reporting.

1

Perspectives

1.1 World Health Organization

AD Bentsi-Enchill,[1] P Duclos,[1] S Pal[2] and P Zuber[1]

Vaccine pharmacovigilance addresses a broad range of issues related to diverse vaccine products and multiple clinical conditions. Defining exposures, measuring outcomes and assessing potential causal relationships between adverse events and the use of specific vaccines can be conducted in different ways, including beyond the rigorously controlled context of pre-licensure[3] studies. This and the variability of definitions used from one clinical trial or surveillance setting to another make comparisons of safety data from different settings and risk-benefit assessments extremely complicated. Individual case reports of adverse events following immunization (AEFIs) in post-licensure vaccine use represent an important source of data as they have the potential to generate signals of adverse reactions not previously recognized in clinical studies.

National post-licensure vaccine safety monitoring systems vary considerably in their structure, methods and performance, with disparities occurring particularly between high-, middle- and low-income countries. Thus offering harmonized tools and methods for vaccine safety monitoring represents a means of facilitating data comparability and exchange across countries.

WHO plays multiple roles in vaccine safety and vaccine pharmacovigilance at the global level:

- WHO provides technical support to its Member States to develop and maintain capacity for post-licensure vaccine safety monitoring as part of countries' responsibility for vaccine regulation and ensuring delivery of safe and effective vaccines. This is mainly conducted by proposing adequate and harmonized approaches; providing training resources for national staff; and ensuring access to up-to-date information about the quality and safety as well as efficacy

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[1] Department of Immunization, Vaccines and Biologicals, WHO

[2] Department of Essential Medicines and Pharmaceutical Policies, WHO

[3] The terms "approval", "authorization" and "licensure" in the context of vaccine (and drug) regulation in different jurisdictions mean the declaration by a regulatory authority that a product following review was found to have a positive risk/benefit and the product is approved for marketing and use. For consistency, we have adopted "licensure" to cover any of these regulatory procedures or declarations. "Marketing" (or "post-marketing", etc.) is usually used to describe the phase of vaccine distribution following the manufacturer›s decision to market the vaccine. The manufacturer may decide not to market a product even though licensure has been granted by the regulatory authority. While "marketing" differs in meaning, we have adopted, for consistency, the term "post-licensure" throughout this report to include everything that follows licensing of the product (i.e., "post-licensure" includes post-marketing considerations that would apply in the specific context in which the term is used).

and effectiveness of vaccine products. Given the global disparities in vaccine safety monitoring systems, WHO's priority support is directed towards low- and middle-income countries.

- WHO provides advice to Member States about vaccine safety concerns of global, regional or national importance. This is performed primarily through a review of the scientific evidence by the independent Global Advisory Committee on Vaccine Safety (GACVS).

- WHO can also be a resource for its Member States to provide technical support for the investigation of vaccine safety issues in order to minimize any potential risks to vaccinated persons while avoiding unnecessary disruptions to the immunization programmes.

- WHO has the unique role to provide advice to United Nations (UN) agencies on the acceptability of vaccines for purchase, in most cases for supply to low- and middle- income countries. This service is provided through the WHO vaccine pre-qualification scheme whose aim is to ensure that vaccines provided through UN supply are safe and effective. Vaccine pre-qualification by WHO is based on quality, safety and efficacy information from pre-licensure studies and, as available, safety and effectiveness data from post-licensure use. Low- and middle-income countries are the primary users of pre-qualified vaccines, and the post-licensure surveillance of those products is dependent on the performance of vaccine pharmacovigilance systems in those countries.

- WHO operates the Programme for International Drug Monitoring (through its Collaborating Centre, the Uppsala Monitoring Centre (UMC), http://www.who-umc.org/). This programme maintains a global database of adverse drug reactions, including those for vaccines. Data from more than 100 participating countries – albeit currently limited for vaccines compared to drugs – are pooled, enhancing the ability for early detection of safety signals that could not be recognized by individual countries.

The outputs of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance such as the generic definitions of terms used in vaccine pharmacovigilance, the endorsement of the Brighton Collaboration case definitions, and dissemination of reference documents in several languages, will help harmonize vaccine safety monitoring methods and result in the generation of better scientific data to further enhance our understanding of

the safety profile of vaccines. The outputs of the Working Group, and the dedication of its members and their organizations, therefore provides an invaluable global contribution and will facilitate WHO's efforts in all the areas mentioned above. This contribution falls within one of WHO's core mandate, which is to issue global norms and standards.

In the current global context, reports of real or alleged vaccine-related adverse reactions raised in one country (or a few countries) tend increasingly to have significant impact on the acceptance of a vaccine product and even on public confidence in whole national immunization programmes. The optimal conduct of vaccine pharmacovigilance at the highest levels is therefore of paramount importance to all stakeholders convened by this Working Group, including vaccine safety experts from industrialized and emerging countries, from public and private sectors, as well as academic experts. This work therefore demonstrates the ability to join forces and harness a broad range of expertise and perspectives to resolve issues of common interest.

WHO's role in supporting its Member States extends to ensuring that the outputs of this work are made readily accessible and put to practical use. This will require their inclusion into training materials, ensuring consistency with and updating of other resource materials, and translation and dissemination through WHO channels. All stakeholders of the Working Group will need to continue active efforts towards the dissemination and utilization of the products of the collective contribution.

One gap recognized throughout the deliberations of this Working Group is the challenge of ensuring consistent and accurate use of standard terms and definitions (developed in one language) across many languages. The development of an international glossary of vaccine safety terminology would help to address accessibility and use of already developed terminology as well as providing a reference for future materials.

1.2 Vaccine Regulatory Authorities

P Bahri,[1] R Ball,[2] M Freitas Dias,[3] B Keller-Stanislawski[4] and X Kurz[1]

The safety of vaccines benefits from regulations for marketing authorization and post-licensure supervision as do all other medicines. Their

[1] European Medicines Agency
[2] US Food and Drug Administration
[3] Agência Nacional de Vigilância Sanitária (Brazil)
[4] Paul-Ehrlich-Institut (Germany)

implementation for vaccines is however of special importance and needs to take into account a number of specific aspects.

The special importance of vaccine safety must be understood in the context of acknowledging immunization as one of the major successful public health interventions worldwide, protecting populations from some of the most health-impairing infections. One of its biggest successes lies in the protection of children from so-called childhood diseases, some of which are potentially fatal or permanently disabling, such as measles and polio. Vaccines work through protection of the individual as well as at the population level, e.g. through herd immunity or eradication of the infectious agent. This means that the benefit-risk assessment has to consider both these levels of benefit in relation to any possible risks. Vaccines are usually administered to healthy individuals, often young children, for prophylaxis and demand the highest safety standards.

This important contribution of vaccines to public health explains the high expectations from individuals and society for effective and safe vaccines. In this context, expectations reflect all different aspects of being personally concerned, possibly worried for safety and uncertain about conflicting information, while there is eagerness for a maximum health benefit.

Consequently, a special focus on vaccines within pharmacovigilance in regulatory authorities is required. Systems put in place for the collection of adverse event data, either through spontaneous reporting or organized data collection schemes, should take into account the specifics of the manufacturing, distribution and delivery of vaccines within health-care systems. The assessment of adverse events and their possible causal relationship with the respective vaccine as well as the signal detection process demand specific knowledge. Some adverse events are of particular concern for vaccines. Because of the high safety standards, serious adverse reactions to vaccines are normally rare. Hence timely data collection from large populations, sometimes from more than one country, is necessary to detect and analyse any problem. Data collection should ideally be planned in a proactive approach to pharmacovigilance and benefit-risk management long before a product launch.

Other aspects justifying a special focus on vaccines within pharmacovigilance at the regulatory level are their vulnerability to quality problems and immunization errors such as cold chain interruption. Quality problems and immunization errors may lead to patient harm, both in terms of adverse reactions as well as due to vaccination failure. Pharmacovigilance for vac-

cines must hence have a broad view and involve timely and efficient collaboration of all parties in problem solving.

Fundamental to minimizing risks and maximizing benefits of vaccines is participation of all involved parties, including vaccine users, i.e. vaccine providers and potential vaccinees and/or their carers. Reporting of adverse events and user-friendly product information are crucial but not the only elements in this respect. Participation of stakeholders in vaccine pharmacovigilance will follow different models in various jurisdictions, depending on regulations, policies and expectations of the public. Independent from the model, however, the need for engagement and communication between regulators and those using or recommending vaccines will remain fundamental to the continued success of immunization strategies. Moreover, vaccine pharmacovigilance requires international collaboration at all stages, from data collection to risk assessment to problem solving.

A common technical language is therefore essential, not only in relation to case definitions of what clinical signs and symptoms constitute a specific adverse event, but also in relation to general terminology. Moreover, common principles for the conduct of vaccine pharmacovigilance will support collaboration among stakeholders, in particular when collecting and comparing adverse event data and performing risk management worldwide. WHO and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have defined general terms for pharmacovigilance and developed the medical dictionaries WHO Adverse Reaction Terminology (WHO-ART) and the ICH Medical Dictionary for Regulatory Activities (MedDRA) for coding adverse event data. It remains however important to continue discussing how these general terms should be interpreted for vaccine pharmacovigilance, whilst ensuring the consistency of terms and processes across pharmacovigilance for all medicinal products. The terms for adverse reactions contained in the dictionaries are grouped within a hierarchical structure, and Standardized MedDRA Queries (SMQs) have been developed for retrieving MedDRA-coded adverse event reports by grouping terms that relate to a medical condition or area of interest. Applying SMQs to vaccines is of interest to regulatory agencies. These major advancements have been complemented by the Brighton Collaboration by means of AEFI case definitions.

Therefore, from a regulatory perspective, thanks need to be expressed to the Brighton Collaboration for their vision and initiative and to CIOMS

and WHO for taking these further at the international level. The terminology and principles for vaccine pharmacovigilance agreed by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance should promote the development of safe vaccines and their appropriate use, so that the success achieved with immunization as a practical, trusted, safe and effective public health intervention continues. Fostering this success and hence protecting lives are the expectations of the public that regulators are committed to fulfil.

1.3 Vaccine Industry

NS Bachtiar,[1] S Bailey,[2] M Blum,[3] A Dana,[4] K Hartmann,[5] SS Jadhav,[6] E Matos dos Santos,[7] J Premmereur,[8] F Sillan[9] and H Seifert[10]

Vaccine pharmacovigilance is a critical and essential component of vaccine safety, which is a key responsibility of all the stakeholders involved in providing vaccines to the public. Implementing the highest quality vaccine pharmacovigilance system to deliver safe vaccines is a top priority for the vaccine industry.

Industry finds great value in the work of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance. The Working Group has allowed representatives from academia, regulatory authorities, public health agencies, and industry to come together in a highly collaborative and open forum. This provides a platform for open dialogue and intellectual discussion with a common goal of a comprehensive, high-quality vaccine pharmacovigilance system. In addition, the Working Group provides a forum for vaccine manufacturers in developed and developing countries to share their perspectives on vaccine pharmacovigilance conducted by industry.

A robust pharmacovigilance system is not possible without common terminology and definitions. The work of the CIOMS/WHO Working

1 PT Bio Farma
2 Pfizer
3 Wyeth Research
4 Merck & Co., Inc.
5 Crucell/Berna Biotech Ltd
6 Serum Institute of India Ltd
7 Bio-Manguinhos/FIOCRUZ
8 Novartis
9 Sanofi Pasteur
10 GlaxoSmithKline Biologicals

Group on Vaccine Pharmacovigilance has advanced the use of standards, and serves as a model for such standardization across all vaccine products.

Industry contributes to vaccine pharmacovigilance by bringing specialized product knowledge to this critical task. This includes a deep understanding of vaccines throughout their life cycle, from early development to post-licensure activities. Industry generates toxicology, animal data and other related information for understanding the safety profile of a vaccine and has access to the scientists who have worked on a product from its very inception through the manufacturing processes. Finally, industry is involved in many important post-licensure data sources, including epidemiologic studies, registries, patient surveys, and patient exposure data.

In collaboration with other key stakeholders, industry's contributions to global vaccine pharmacovigilance include:

- Pharmacovigilance professionals dedicated to monitoring the safety of vaccines, with a deep insight into the safety profile and history of the vaccine.
- Identification and investigation of manufacturing quality concerns, including review of data by lot and batch[1] to find any product quality issues, even if they arise after the product is released and distributed.
- Tracking and investigation of product complaints, even those without adverse events.
- Targeted, proactive review of safety data in real time and active signal detection.
- An important perspective in terms of risk management, minimization, prevention and communication.

Industry has a critical role in information flow, receiving feedback from patients and providers, and providing information on the appropriate use of their products in return. These communication channels can enhance pharmacovigilance, including medical information communications and collection of adverse event follow-up data.

Clearly, the work of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance has already proven valuable to pharmacovigilance efforts by industry, particularly the endorsement of standardized AEFI case

[1] While it is acknowledged that different jurisdictions use the terms "vaccine lot" and "vaccine batch" differently, they are used interchangeably in this report.

definitions developed by the Brighton Collaboration. Thanks to the standard encouraged by the Working Group in understanding potential cases of Guillain-Barré syndrome (GBS), there was the ability to provide high-quality adjudication of reports and better understanding of this issue during pandemic influenza A/H1N1 vaccine monitoring. Further, work on MedDRA mapping, resulting in the development of new SMQs and modification of existing SMQs based on Brighton Collaboration definitions, should improve the ability to retrieve AEFI cases from industry and other databases.

Industry greatly appreciates the important role the CIOMS/WHO Working Group on Vaccine Pharmacovigilance has played in improving the safe and appropriate use of vaccines throughout the world. As seen by the many improvements in the standardization of terminology in which the Working Group has been vital, it has contributed to a series of practical improvements of vaccine pharmacovigilance. The cooperation and collaboration between key stakeholders which it fosters is vital to the continued improvement of vaccine pharmacovigilance and the continued protection of the public.

1.4 Public Health Agencies and Academia

A Dodoo,[1] J Gidudu,[2] U Heininger[3] and B Law[4]

Immunization has been touted as one of the most significant medical advances of the 20th century and is a major cornerstone of public health. The continued success of immunization programmes in preventing disease and promoting public health depends to a great extent on high levels of vaccine coverage among targeted population groups. In turn, coverage rates are impacted by stakeholder perceptions regarding vaccine safety, especially those held by the public and health-care providers. There is a need for clarity, knowledge translation and education regarding pharmacovigilance practices and data as they relate to vaccines. Thus highlighting the unique aspects of vaccines relative to therapeutic products and developing specific definitions for several key concepts such as AEFI and vaccination failure are of prime importance from both a public health and academic perspective.

[1] University of Ghana Medical School
[2] US Centers for Disease Control and Prevention
[3] University Children's Hospital, Basel, Switzerland
[4] Public Health Agency of Canada

A major challenge to assessing and communicating safety from the earliest stages of vaccine development to monitoring in the post-licensure phase has been the lack of a standard "vocabulary" or definitions for adverse events including rare events that may be associated with vaccines (e.g. seizure, thrombocytopenia, GBS) and also relatively common side effects such as fever or injection site inflammation. Standardized definitions and terminology were an invaluable resource for the global community during safety monitoring of influenza A/H1N1 vaccines in 2009-2010 and permitted sharing of information obtained from multiple vaccine safety surveillance systems. Sharing data on adverse events is problematic if, due to the absence of standardized definitions and terminology, one cannot be relatively sure that the events are as described. The Brighton Collaboration (https://brightoncollaboration.org/public) has been highly productive over the last decade in producing, with painstaking attention to detail and process, 25 published standard definitions for a wide variety of AEFIs and guidelines for their use. Furthermore, validation studies of some of the case definitions have been performed by academic groups, including members of the Brighton Collaboration, and some of those studies have led to revisions of the case definitions (anaphylaxis in progress, and hypotonic-hyporesponsive episode (HHE) completed).

In this regard, the efforts of the WHO/CIOMS Working Group on Vaccine Pharmacovigilance related to reviewing, endorsing, translating and suggesting additional Brighton Collaboration AEFI case definitions are of great importance from both the public health and academic perspectives.

The use of standardized criteria and terminology in signal generation is familiar to those working in general pharmacovigilance. In contrast, the field of vaccine pharmacovigilance lacks well-harmonized terms and concepts. An important task of the Working Group is to ensure that the public health and academic communities are aware of and apply, when appropriate, the output from this Working Group and other CIOMS working groups that relate to pharmacovigilance.

This report developed by the Working Group can be used as:

- a resource for initial and continuing health professional education related to vaccine pharmacovigilance and AEFI reporting;
- a resource for education and risk communication related to vaccine pharmacovigilance; and

- a reference for global application of standard AEFI definitions in clinical trials and epidemiologic study settings and in post-licensure surveillance settings.

Publication of case definitions for AEFIs is a necessary but unfortunately insufficient requirement for their global application. It is therefore important to also:

- ensure appropriate widespread dissemination and implementation of the case definitions;
- incorporate them in training materials; and
- conduct further validation studies for applicability in various settings.

Public health agencies and academia should give consideration to MedDRA terms and SMQs in the process of developing standard Brighton Collaboration AEFI case definitions.

In an era where most vaccine-preventable diseases are no longer common, safety concerns, even unproven ones, have become increasingly prominent, especially in relation to new and combination vaccines. Continued effort to earn and maintain public trust is critical. This can be achieved only if there is global sharing of information on vaccine safety, a task that requires globally accepted standards.

2

Background and scope of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance

2.1 Rationale for creation of the Working Group

The CIOMS/WHO Working Group on Vaccine Pharmacovigilance was established in November 2005 as a joint initiative of WHO and CIOMS to meet specific needs identified for vaccine pharmacovigilance.

The Working Group constituted the fifth collaborative group to be formed by CIOMS to address drug safety issues, in this case for vaccines. In establishing this joint working group, both WHO and CIOMS recognized that vaccines represent a somewhat special group of medicinal products, and that there was a need to focus on addressing issues specific to the monitoring and assessment of vaccine safety. Several factors in the development of vaccines and the settings of post-licensure vaccine use were highlighted by the Working Group from its inception as issues for special consideration and continued to define and guide the work of the group as is reflected in this report. Particular attention was given to the need to harmonize terms and concepts for use in the conduct of vaccine pharmacovigilance by all relevant parties. In particular, the Brighton Collaboration (https://brightoncollaboration.org/public) was the unique initiative in the area of developing standardized case definitions for AEFIs, and this became a strong focus for the Working Group's goals.

A primary objective of the Working Group was critical contribution to the development, review, evaluation, and endorsement of AEFI case definitions developed by the Brighton Collaboration. The scope of contribution was defined to cover previously published case definitions as well as those under development or yet to be developed. The Working Group also wished to contribute to the dissemination of those case definitions, including supporting their translation in additional languages other than English.

A second objective of the Working Group was to develop standardized definitions and terminology or other guidance documents relevant to vaccine safety that would contribute to harmonizing vaccine pharmacovigilance among different stakeholder groups or relevant parties. The Working Group sought to meet this objective in two ways: through reference to terms and definitions already developed by other organizations or bodies and through representation of those organizations and bodies in the Working Group membership.

2.2 Terms of reference

Members of the Working Group at its inaugural meeting discussed the proposed terms of reference and finalized them as follows:

(i) To propose standardized definitions relevant to the monitoring of safety of vaccines intended for the prevention of infectious diseases during clinical trials and for the purposes of vaccine pharmacovigilance in the post-licensure period.
(ii) To contribute to the development, review, evaluation, and approval of case definitions on AEFIs as developed by the Brighton Collaboration process and contribute to their dissemination (including their translation in additional languages).
(iii) To collaborate with other CIOMS Working Groups, especially that on SMQs and CIOMS Working Group VIII on Signal Detection on issues relevant to vaccine safety.

The Working Group has worked on increasing awareness and dissemination of the general guidelines developed by the Brighton Collaboration for collection, analysis and presentation of vaccine safety data in clinical studies and surveillance systems.

Additional activities the Working Group engaged in, while not formally included in its terms of reference, included providing consultations and expert inputs to other vaccine pharmacovigilance initiatives such as the Global Vaccine Safety Blueprint project led by WHO and the development of a vaccine dictionary by the UMC.

2.3 Membership

The Working Group was initiated with 22 members invited by WHO and CIOMS from the vaccine industry, regulatory agencies, national and international public health agencies including WHO and CIOMS, and academia. The terms *stakeholders* and *stakeholder groups* as used in this report reflect this composition of the Working Group. The members of the Working Group during its 5-year tenure are listed in Annex 1.

2.4 Mode of operation

The Working Group accomplished its work primarily by face-to-face meetings (two meetings a year) as well as interaction among members between meetings to carry out specific assigned work. A number of subgroups (of three or more persons with at least one representative each from the private and public sectors) were established to prepare specific definitions or to work on agreed upon topics under the lead of a subgroup leader. Outputs of the subgroups' work were presented to the full Working Group for review and endorsement, usually during the face-to-face meetings.

3

General definitions

The general definitions and discussion papers developed by the Working Group, and presented in this section, were developed over varying periods during 2005 to 2010. Each definition, set of related definitions, or paper was developed with active participation by a subgroup of the membership (as described in section 2.4) and the final product endorsed by the full Working Group as published in this report. The development process of each product varied according to the nature and complexity of the product and is briefly summarized below.

Vaccine pharmacovigilance: This case definition was finalized and endorsed by the Working Group in October 2007 and disseminated through the CIOMS website and a number of relevant scientific presentations and materials. An updated definition has been introduced as part of this report (see section 3.1).

Vaccination failure: A concept of vaccination failure was initially endorsed by the Working Group in April 2008 and published on the CIOMS website. An update, supplemented with specific examples, an algorithm and a data checklist is included with this report (see section 3.2).

AEFI definitions: The need to develop these general terms was identified at the first meeting of the Working Group in November 2005 and the process of development progressed in parallel with other activities of the Working Group. Due to the complexity of the terms and definitions, extensive consultation both within the Working Group and with external experts was undertaken. This set of definitions has not been published prior to this report (see section 3.3).

Points to consider regarding differences between vaccines and drugs in signal detection: At its October 2007 meeting, this Working Group took note of the work being undertaken by the CIOMS Working Group VIII on Signal Detection and determined that there was no need to develop a separate definition of "signal" for vaccine pharmacovigilance. Rather, the Working Group requested that key considerations for vaccine signal detection be prepared for inclusion in the CIOMS VIII report. The final report by this Working Group on the points to consider for vaccine signal detection was endorsed in April 2008 and submitted for inclusion as an annex in the Report of the CIOMS Working Group VIII on Signal Detection (*1*). Editorial changes to those points have been included in this report (see section 3.4). Further, the definition of a signal by the CIOMS Working Group VIII is hereby adopted for this report (see Glossary and section 3.4).

3.1 Vaccine pharmacovigilance

3.1.1 Preamble

The terms of reference for the CIOMS/WHO Working Group on Vaccine Pharmacovigilance included the development of standardized definitions relevant to the monitoring of the safety of vaccines during clinical trials and for the purposes of vaccine pharmacovigilance in the post-licensure period.

3.1.2 Definition

Vaccine pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and communication of adverse events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.

3.1.3 Explanatory notes and comment

The goal of vaccine pharmacovigilance is the early detection of and appropriate and timely response to AEFIs in order to minimize negative effects to the health of individuals and lessen the potential negative impact on immunization of the population. Continuous risk-benefit assessment and risk management are integral to the vaccine pharmacovigilance process.

There is a very high level of safety required for vaccines. Elements to consider when conducting vaccine pharmacovigilance include the following:

- Vaccines are usually administered to healthy people, including infants.
- Vaccines may be administered to the vast majority of the population or of a birth cohort or to groups at high risk for disease complications.
- Subpopulations may be more susceptible to experience certain AEFIs (*2*).
- The age at the time of immunization may coincide with the emergence of certain age-related diseases (e.g. neurodevelopmental disorders).
- Immunization with certain vaccines is mandated in some countries.

- The benefits of immunization may not be immediately visible, particularly if the target disease incidence is low.
- Due to the low acceptance of risks, intensive investigation of serious AEFIs, even if rare, is necessary (*3*).
- Non-serious AEFIs also should be carefully monitored because they may signal a potentially larger problem with the vaccine or immunization, or have an impact on the acceptability of immunization in general.
- Appropriate methods are needed to detect and assess any potential causal association of serious, rare, and/or delayed adverse events, or of adverse events in subgroups, with immunization.
- Consideration of dechallenge and rechallenge differs for vaccines compared with other medicinal products. Vaccines are frequently administered only once or with long intervals, and serious AEFIs often prevent further vaccine administration; hence rechallenge information is only rarely available. Dechallenge may not be applicable to vaccines, given their long-term immunological effects.
- Vaccines are often administered concomitantly with other vaccines, making causal attribution to a specific vaccine difficult.
- The administration of live vaccines can lead to disease caused by the attenuated organisms in vaccinees or their contacts; this should be differentiated from coinciding natural infection (*4*).
- Vaccines are complex biological products, which may include multiple antigens, live organisms, adjuvants, and preservatives. Each component may have unique safety implications. Variability and (even small) changes in the manufacturing process may have impact on quality, protective effect, and safety. Batch information is of crucial importance.
- New vaccines are increasingly based on new production and administration technologies, with new adjuvants and alternative routes of administration, necessitating adapted safety monitoring systems (*5*).
- Depending on the mode and extent of use of a vaccine, it may elicit a degree of herd immunity to a specific disease. When assessing the risk-benefit of a vaccine, herd immunity effects as well as individual protection need to be taken into account (*6*).

- Effective communication regarding the safety of vaccines and immunization is challenging. Despite strong evidence that a serious adverse event is not related to immunization, perceptions of harm may persist and may potentially have a negative impact on immunization of the population (*7, 8*).

3.2 Vaccination failure

3.2.1 Introduction

The development of sustainable immunization programmes delivering safe and effective vaccines to human populations has been proven to be highly successful (*9, 10, 11, 12*). However, vaccines are neither 100% efficacious nor 100% effective (where efficacy is determined in clinical trials, usually pre-licensure, and effectiveness is determined in practical use, i.e. post-licensure) (*13, 14, 15*).

Various case definitions for vaccination failure are being used in different settings, e.g. for reporting to regulatory authorities or in epidemiological studies. Vaccination failure can be defined by a variety of endpoint criteria (e.g. disease prevention, disease mitigation or immune response) (*16, 17, 18, 19*). Different terms are also used inconsistently to designate vaccination failure, e.g. lack of vaccine efficacy or lack of adequate protection (*20, 21*). Universally accepted concepts and definitions of vaccination failure are therefore required to assess and compare the benefit of vaccines.

A major issue regarding any definition of vaccination failure is the question of the clinical endpoint against which a specific vaccine should protect, i.e. infection versus disease versus serious (complicated) disease. These issues could potentially be solved by proposing general definitions for types of vaccination failure complemented by specific definitions for a given vaccine.

3.2.2 Vaccination failure: vaccine failure or failure to vaccinate

Vaccination failure may be defined based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist (*22, 23*). Primary failure (for example, lack of seroconversion or seroprotection) needs to be distinguished from secondary failure (waning immunity).

Vaccination failure can be due to 1) vaccine failure or 2) failure to vaccinate, i.e. that an indicated vaccine was not administered appropriately for any reason (Figure 1).

Reasons for vaccination failure are manifold and include, but are not restricted to, the following.

A. Vaccine failure

(1) Vaccinee-related (host-related):

(a) *immunodeficiency* (leading to suboptimal or even absent immune response after vaccination);
(b) *age-related maturation and senescence of immune responsiveness;*
(c) *insufficient or suboptimal immune response* (other than a defined immunodeficiency) to one or more antigenic vaccine components or vaccine strains or serotypes; this may or may not be measurable by standard laboratory tests such as serum antibody tests;
(d) *interference due to other infectious agents* (e.g. wild type enterovirus infection causing interference with the immune response to oral poliomyelitis vaccine (OPV));
(e) *waning immunity;*
(f) *suboptimal health status* (e.g. underlying disease, nutrition);
(g) *immunological interference* (e.g. maternal antibodies, administration of immunoglobulins);
(h) *pre-existing infection with pathogen targeted by the vaccine* (e.g. with specific HPV genotypes) or *immunization during incubation period* (after exposure to pathogen);
(i) *immunosuppressive therapy.*

(2) Vaccine-related:

(a) *vaccine is not 100% efficacious against included antigens;*
(b) *incomplete coverage* of strains, serotypes, genotypes, antigenic variants or escape mutants that can cause a vaccine-preventable disease;
(c) *antigenic interference* or other *vaccine-vaccine interactions in case of co-administered vaccines;*
(d) *manufacturing-related* (e.g. batch variations, quality defect).

B. Failure to vaccinate

(3) Usage issues:

(a) *administration error* (wrong or suboptimal route, inadequate dose, incorrect diluent);
(b) *vaccination series incomplete, non-compliance with recommended schedule, including lack of recommended booster vaccination(s)* ("failure to vaccinate" rather than "vaccination failure");

(c) *storage-related (e.g. cold chain);*
(d) *vaccine beyond expiry date* when used.

(4) Immunization programme-related issues:

(a) *suboptimal recommendations* regarding number and time points of primary and/or booster vaccinations;
(b) *shortage of vaccine* leading to no or incomplete vaccination (see also (3) b.).

One or more of these reasons listed under vaccine failure (section 3.2.2, A) or failure to vaccinate (section 3.2.2, B) may lead to individual vaccination failure. They are *not* part of a case definition and may or may not be discovered in the process of analysing individual suspected vaccination failure. A data checklist to aid in collecting data that can help identify reasons for vaccination failure in an individual is provided (see Annex 3, *Data collection checklist for suspected vaccination failure*).

3.2.3 Definitions of vaccine failure

As stated above, each specific vaccine has a specific prophylactic goal and is used with a specific intent which may be country- or programme-specific. As such, there needs to be a specific definition for vaccine failure which is applicable to that specific vaccine. However, general definitions for vaccine failure can be proposed and confirmed vaccine failure needs to be distinguished from suspected vaccine failure.

The following are proposed general definitions.

A. Confirmed clinical vaccine failure

The occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunization.

The application of this definition requires clinical and laboratory confirmation (or epidemiological link to a confirmed case, where applicable) that the actual disease is vaccine preventable, i.e. that the pathogen (including, where appropriate, type, subtype, variant, etc.) and clinical manifestations are specifically targeted by the vaccine.

- Example (consistent with clinical vaccine failure): Report of a 60-year-old patient who received one dose of 23-valent pneumococcal polysaccharide vaccine and who is diagnosed with bacterae-

mic pneumonia with *S. pneumoniae* Type 19F six months later. In this case the patient was appropriately immunized, and he got sick at a time when he should have mounted an immunologic response to the vaccine. In addition, his exposure would have been at a time that protection could have been expected as the incubation period for pneumococcal disease is probably days to perhaps weeks.

- Example (inconsistent with clinical vaccine failure): Report of a 23-year-old patient, recently vaccinated with hepatitis B vaccine on a schedule of 0, 1, and 6 months. The patient developed jaundice and fever two weeks after the last dose and was found to be anti-HBc-IgM and HBsAg positive. In this case, although the patient was appropriately immunized, his exposure to the hepatitis B virus must have occurred prior to the complete vaccination series based on the incubation of the infection (2-6 months). Because protection would not be expected to have been reliably achieved prior to exposure or infection this would *not* be considered a vaccine failure.

B. Suspected clinical vaccine failure

Suspected vaccine failure is defined as the occurrence of disease in an appropriately and fully vaccinated person, but the disease is not confirmed to be the specific vaccine-preventable disease, e.g. invasive pneumococcal disease of unknown serotype in a fully vaccinated person. Applying this definition also requires that the incubation period and the normal delay for the protection to be acquired as a result of immunization have been taken into account.

- Example (consistent with suspected clinical vaccine failure): A 2-year-old boy received four doses of *Haemophilus influenzae* type B conjugate vaccine at 2, 4, 6 and 12 months of age. He develops bacteraemia with *H. influenzae*, but no serotyping is performed on the organism. In this case the patient is fully and appropriately immunized and the exposure should have occurred at a time when protection would be expected based on incubation and time to response. However, it is not clear that the disease was caused by *H. influenzae* type B, i.e. that it would have been preventable by the vaccine.

C. Confirmed immunological vaccine failure

In addition to clinical vaccine failure, there is the possibility of immunological vaccine failure, not necessarily associated with a clinical manifestation of the vaccine-preventable disease. Immunological failure is

defined as failure of the vaccinee to develop the accepted marker of protective immune response after being fully and appropriately vaccinated. This definition requires that there is an accepted correlate or marker for protection, and that the vaccinee has been tested or examined at an appropriate time interval after completion of immunization.

Example (consistent with immunological vaccine failure): A 32-year-old health-care worker received three doses of hepatitis B vaccine on a schedule of 0, 1 and 6 months and anti-HBs antibody testing of her serum six weeks after the third dose revealed a value of <10 U/l. This health-care worker was considered an immunological failure of hepatitis B vaccination.

D. Suspected immunological vaccine failure

Example (inconsistent with immunological vaccine failure): Same situation as above apart from anti-HBs antibody testing being done only eight years after the third dose with a value of <10 U/l. Since the time interval of antibody testing was inappropriate, immunological failure is possible but was not confirmed as such.

3.2.4 Need for vaccine-specific definitions of vaccine failure

Circumstances for incomplete protection of an individual after appropriate immunization are vaccine-specific (and, where appropriate, programme-specific) and therefore vaccine-specific (or programme-specific) definitions are needed. The following items need to be considered in the process of developing such definitions:

- what is the vaccine supposed to prevent (infection, any severity of disease, or severe disease)?
- which other known causes may lead to the same or similar clinical endpoints as those caused by the vaccine-preventable pathogens and how can they be distinguished?
- when is full protection expected during the time course of immunization?
- what is the incubation period for the specific targeted pathogen and what is the time period after vaccination that the onset of the disease actually represents exposure to the pathogen prior to vaccination?

A specific vaccine may fail to prevent various degrees of individual disease and therefore clinical relevance of vaccine failure may vary. This could be addressed by the development of definitions for different levels of vaccine failure for specific types of vaccine depending on the immunization goal.

3.2.5 Conclusions

Vaccination failure may be due to actual vaccine failure or failure to vaccinate appropriately. The reasons mentioned above require the development of vaccine-specific definitions for vaccine failure, where many individual factors need to be taken into account. This discussion of vaccination failure can serve as a basis for the development of such definitions.

Case definitions for vaccine failure of specific types of vaccine should be prioritized based on public health considerations.

3.3 Adverse events following immunization

3.3.1 Preamble

The terms of reference for the CIOMS/WHO Working Group on Vaccine Pharmacovigilance included the development of definitions relevant to the monitoring of the safety of vaccines during clinical trials and for the purposes of vaccine pharmacovigilance in the post-licensure period. Specifically, these included AEFI definitions which are presented below. The approach to the AEFI definitions was developed at the first meeting of the Working Group in November 2005 and included the intent to define AEFI in general as well as to define several specific terms based on cause. It was also decided that the definitions would be consistent with established ICH and UMC definitions of *adverse event* and *adverse reaction*.

These definitions and related information are laid out in three parts:

- AEFI general and cause-specific definitions and associated concepts;
- explanatory notes regarding the contextual application of the definitions; and
- lists of underlying mechanisms for each AEFI cause-specific definition. The lists are meant to be illustrative, not exhaustive.

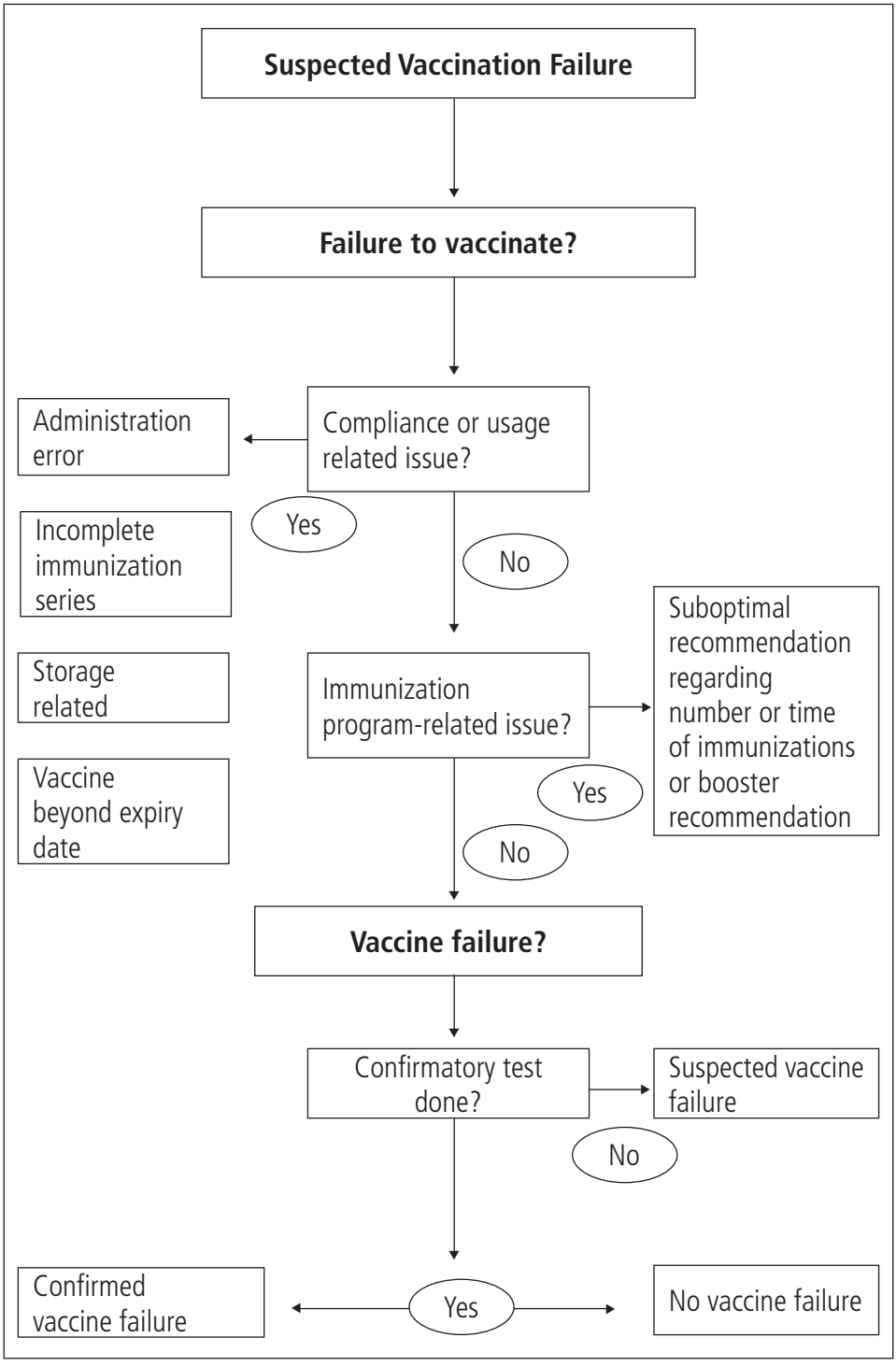
3.3.2 Definitions for AEFI

A. General definition

Adverse event following immunization[1] ***(AEFI):*** any untoward medical occurrence which follows immunization and which does not necessarily

[1] "Immunization" as used in these definitions means the usage of a vaccine for the purpose of immunizing individuals. "Usage" includes all processes that occur after a vaccine product has left the manufacturing/packaging site, i.e. handling, prescribing and administration of the vaccine.

Figure 1: Vaccination failure algorithm



have a causal relationship with the usagea of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

B. Cause-specific definitions

1. ***Vaccine product-related reaction:*** An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.

2. ***Vaccine quality defect-related reaction:*** An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects[1] of the vaccine product including its administration device as provided by the manufacturer.

3. ***Immunization error-related reaction:*** An AEFI that is caused by inappropriate[2] vaccine handling, prescribing or administration and thus by its nature is preventable.

4. ***Immunization anxiety-related reaction:*** An AEFI arising from anxiety about the immunization.

5. ***Coincidental event:*** An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.

C. Related definitions:

Serious adverse event: This concept is defined by ICH in the ICH E2A and E2D guidelines (*24, 25*). Seriousness is based on patient/event outcome or action criteria and defines regulatory reporting obligations. An AEFI will be considered serious if it results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. The ICH E2A and E2D guidelines also state that other situations, such as other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes above, should also be considered serious after applying medical and scientific judgment. Those "other situations" are open to interpretation and could vary from jurisdiction to jurisdiction. It is important to note that

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[1] For the purpose of this report, a vaccine quality defect is defined as any deviation of the vaccine product as manufactured from its set quality specifications.

[2] "Inappropriate" refers to usage (handling, prescribing and administration) other than what is licensed and recommended in a given jurisdiction based on scientific evidence or expert recommendations.

'serious' and 'severe' are often used as interchangeable terms but they are not. Severe is used to describe the intensity of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance.

The criteria for seriousness have been discussed in the CIOMS V report on *Current Challenges in Pharmacovigilance* (*26*). The application of the criteria is dependent on their interpretation and health practices in a particular setting. For example, variability in hospital admission practices may result in observed differences in the proportion of reported serious and non-serious events in different settings and databases.

3.3.3 Contextual applications of the general and cause-specific definitions

Having both general and cause-specific AEFI definitions is consistent with the multiple perspectives inherent in vaccine pharmacovigilance. As discussed further below, the context in which an AEFI is considered impacts on whether the general definition is most applicable or if one or more cause-specific definitions should be considered. The relevant settings include:

- AEFI reporting from organized data collection systems
- Spontaneous AEFI reporting
- Individual AEFI case assessment and management
- AEFI cluster investigation
- AEFI causality assessment
- AEFI and vaccine safety communication and education

AEFI reporting from organized data collection systems: Generally, organized data collection systems include clinical trials, registries, named patient use programmes[1], other patient support and disease management programmes, surveys of patients or health-care providers or information gathering on efficacy or patient compliance (ICH E2D *(25)*). Further, effectiveness studies also gather data in an organized manner. Some of these

[1] "Named patient use" refers to (such as in the European Union) prescription for an individual patient, of a product which is not licensed in that country but is imported specifically for that patient, and for which no storage is allowed normally. In some Member States of the European Union, such prescriptions and import have to be notified to the regulatory (or other specified) authorities. A named patient use programme could also refer to use of a clinical trial product in normal health care with specific authorization (e.g. authorized experimental use in terminally ill patients).

systems are used for vaccine pharmacovigilance. The general and cause-specific definitions for AEFIs are applicable.

Spontaneous AEFI reporting: To support the application of the general and cause-specific definitions in the context of spontaneous AEFI reporting it is important to understand the purpose and processes of spontaneous AEFI reporting (*27*). The primary purpose of spontaneous reporting is to identify safety signals after a product is marketed. While proof of product safety and efficacy are required for licensure, rare or very rare reactions may not be detectable until a product is used in a population setting. Of further relevance to vaccines, as complex biological products, while every effort is made to ensure each lot of vaccine matches the lots used in the studies on which the vaccine product licensure was based, the potential for product variation that could result in a safety signal must always be considered. The ICH E2D guideline (*25*) defines a spontaneous report as "an unsolicited communication by a health-care professional or consumer to a manufacturer, regulatory authority or other organization that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme". This definition applies to AEFI reports as well where a report involves one or more adverse events that follow the administration of one or more vaccines. For regulatory reporting the minimum data elements required include an identifiable reporter, an identifiable patient, an adverse event and a suspect product. The *primary reporter* is the person who first reports an AEFI. In many settings the primary reporter submits a report to an intermediary such as local public health authorities or the vaccine manufacturer who are considered *onward reporters* in that they send the report on to the national regulatory authority. The onward reporters may seek to clarify or expand on the information before sending the report on.

Given the purpose of spontaneous reporting it should be clear that the general definition of AEFI is most relevant to this context since as long as a causal relationship is at least a reasonable possibility, i.e. cannot be ruled out, the AEFI should be reported. In other words suspicion alone is sufficient for reporting and the primary reporter is not expected to assess causality which is implied when considering the cause-specific definitions. Rapid detection and evaluation of safety signals is essential to ensure the continued safety of vaccines. Thus, provided there is suspicion it is preferable to submit a report on a timely basis rather than wait for all aspects of an investigation into the cause to be completed. This is particularly true for reports which meet the criteria to be considered serious reports.

The relevance of the cause-specific definitions to the context of spontaneous reporting is that they emphasize the importance of completeness and accuracy in the original report to the extent possible, as well as the need for follow-up reports. Primary reporters should be encouraged accordingly. Details about the event in question (including specific signs and symptoms) or relevant medical history help to determine whether it meets a case definition such as those developed by the Brighton Collaboration. Reasons for any suspicion that an AEFI may be related to the vaccine product, a vaccine quality defect, an immunization error or immunization anxiety can be included in an AEFI case report by the primary or any onward reporter. Similarly, details regarding concomitant medication or illness or prior conditions in the vaccinee should be included in the primary or follow-up reports because they provide important information for considering whether an AEFI was coincidental or causally related to immunization. It should be noted that some jurisdictions consider lack of efficacy to be an adverse event and thus want vaccination failure (see Section 3.2) to be reported as an AEFI.

Individual AEFI case assessment and management: In the context of clinically assessing an individual with an AEFI, the cause-specific definitions serve as a reminder that the process of differential diagnosis is an integral part of case assessment and management even if a specific cause cannot be determined. For example, thrombocytopenia may be caused by measles-containing live vaccines; however there are many other causes such as infection or concurrent administration of other medicines (coincidental events) and these should be considered when taking a history, examining the patient and deciding on the plan for investigation and management. When a serious event follows administration of a live attenuated vaccine, it is important to remember that recovery of the vaccine strain from a normally sterile tissue sample may allow confirmation of vaccine causation (e.g. recovery of Urabe strain mumps virus from the cerebrospinal fluid of an individual with aseptic meningitis following immunization with measles-mumps-rubella vaccine containing the Urabe mumps strain). In most cases, however, there are no specific tests providing evidence for a causal association between a vaccine and an AEFI. In contrast there may be several tests that can confirm an event is due to a specific cause other than immunization, i.e. a coincidental event. Failure to investigate the underlying cause of an AEFI case, especially if serious, may result in delayed diagnosis of an illness completely unrelated to immunization or may prevent recognition of an underlying condition that could have implications for subsequent im-

munization such as a previously unrecognized immunocompromising condition. The possibility of an AEFI arising because of immunization error must also be considered by individual vaccinators as well as immunization programme managers. (See also discussion on *AEFI causality assessment* below.)

AEFI cluster investigation: Clusters of AEFIs may be identified through spontaneous reporting of AEFIs or organized data collection systems for AEFIs. Cluster has been defined as two or more AEFIs related in time, place and/or by vaccine (*28*). In this definition, vaccine may refer to a certain batch, vaccine product from a certain manufacturer or a vaccine (or vaccines) protecting against a certain strain of the infective agent. The criteria defining a cluster will depend on the context, e.g. for a globally distributed vaccine, the batch may be more important than the place; however in the case of immunization errors, the place will be an important criterion. A cluster can be understood as a special kind of signal, where not only an increase in the AEFI reporting rate has been seen but one or more common characteristics of the AEFI reports have become apparent too. The characteristics are traditionally time, place and/or vaccine, but could also be age group, genetic predisposition, disease or other characteristic of the vaccinees which could constitute a risk factor for a certain AEFI.

When an AEFI cluster has been identified, the cause-specific definitions provide a framework for investigation and causality assessment. Usually the key considerations will be to investigate the possibility of a vaccine quality defect as well as whether an immunization error may have occurred. The possibility of immunization error must be considered when events cluster in one setting without a similar change in frequency in other settings using the same vaccine. On the other hand, if an increased frequency of events is reported from multiple settings the possibility of a quality defect must be considered more strongly. Clusters of fainting after immunization are well-recognized immunization anxiety-related reactions during immunization programmes targeting birth cohorts of adolescent girls. For relatively new vaccines or established vaccines used in new target populations, a cluster may represent a previously unrecognized vaccine product-related reaction. An example of this is when arthritis and arthralgia are first recognized as causally related to rubella vaccine when its use is extended to an adult population in a country that may have had a routine childhood immunization programme. In mass vaccination campaigns coincidental events could appear as a cluster but actually represent the normal background incidence of that event in the population (*29*).

Knowledge of the background incidence of events which may occur in causal relationship with a vaccine is therefore essential for assessing a cluster in terms of the strength of the signal it may provide. In studies with control groups, the incidence of the event in the control group will serve as a comparator. A primary reporter is unlikely to consider a cluster unless the events are obviously linked in time and place, e.g. several cases of fainting, allergic reactions or injection site infections occur within hours in the same health-care setting, or the events are of serious nature such as seizure, encephalitis or even fatal events, occurring over a relatively short time period in a geographical space that the primary reporter may oversee. When AEFIs are reported from multiple health-care settings, it is more likely that the possibility that a cluster may have occurred will be recognised by an onward reporter or the regulatory authority gathering and analysing the AEFI reports.

AEFI causality assessment: Causality assessment of AEFIs may be performed at different levels:

- At the level of the individual AEFI case report, in order to estimate the probability that the occurrence of a reported AEFI in a specific individual is causally related to the usage of the vaccine. It is usually not possible to establish a definite causal relationship between a particular AEFI and a particular vaccine on the basis of a single AEFI case report. Notable exceptions include when an event follows administration of a live attenuated vaccine and the specific vaccine agent is recovered from a normally sterile body site (e.g. osteomyelitis caused by BCG vaccine, aseptic meningitis caused by Urabe strain mumps vaccine virus) or when the same event follows immunization on repeated challenges in the same individual (e.g. a single case report of GBS following each of three doses of tetanus toxoid vaccine administered years apart to the same person was sufficient for the US Institute of Medicine Vaccine Safety Committee (*30*) to consider that a causal relationship between tetanus toxoid and GBS was established).
- At the population level, using data from organized data collection systems and appropriate statistical methodology in order to test the hypothesis that there is a causal association between the usage of a vaccine and a particular AEFI. This may sometimes be combined with causality assessment at the individual level (of AEFIs collected within that system) whereby some or all of the cases of interest

could undergo individual case review and causality assessment before inclusion in a group analysis.

- In the context of the investigation of signals, the assessment of whether a particular vaccine is likely to cause a particular AEFI, takes into account all evidence from individual AEFI cases, organized data collection systems and, where applicable, cluster investigations as well as non-clinical data. (See section 3.4 for a discussion of points to consider in signal detection for vaccines.)

In settings where causality assessment is undertaken it is important to consider all possible explanations for an event and the degree of likelihood for each before addressing the question of whether or not a vaccine product, quality defect, the immunization process or immunization anxiety caused a given event or if it was due to something else such as an inter-current infection. This is true whether the assessment is done for one or multiple cases of an expected or unexpected AEFI. Evidence for a causal link exists for some vaccines and AEFIs (e.g. measles vaccine and thrombocytopenia). This does not ensure, however, that causality can be assessed on an individual basis. Most often this is because of missing or imprecise data in the AEFI report(s) resulting in a case being deemed unclassifiable. In other cases the final designation of an AEFI as to causality may be unknown due to lack of evidence for a causal link. It is still important to gather reports on such events because at some point they may be considered a signal and lead to hypotheses regarding a link between a vaccine and the event in question with specific studies designed to test for a causal association. A good example of this chain of events is spontaneous reports of intussusception following the introduction of bovine tetravalent rotavirus vaccine in the United States (US) that led to several hypothesis-testing studies, evidence for a causal association and ultimately withdrawal of the product's licensure. For causality assessment at the level of study populations, the design and resulting power of the study will be important to evaluate the strength of evidence for the causality. Different methods exist for causality assessment and will be appropriate depending on the nature of the data. This report does not discuss causality assessment further as the Working Group considered a harmonized process for causality assessment to be beyond its scope.

AEFI and vaccine safety communication and education: The proposed general and cause-specific definitions for AEFI can improve understanding as to what an AEFI is and what it is not for all groups concerned,

including health-care and vaccine providers, the general public and the media. As such, the definitions serve as an educational tool for those responsible to communicate with the public or health-care professionals about vaccine safety. For example, members of the public and health-care professionals may perceive AEFI case reports to a spontaneous reporting system like the US Vaccine Adverse Event Reporting System (VAERS) ( ) as evidence of a causal relationship between a vaccine and an AEFI. However, the general AEFI definition points out that an AEFI does not necessarily have a causal relationship with usage of the vaccine. Further, the cause-specific definitions provide a framework to communicate that reported AEFIs may have several underlying causes.

3.3.4 Underlying mechanisms for AEFIs according to cause-specific definitions

The following section lists several possible mechanisms for each of the AEFI cause-specific definitions (see Section 3.3.2.B). While not meant to be exhaustive, the lists should facilitate understanding of the mechanisms or processes possibly underlying each of the defined AEFI causes. Further, they provide a framework applicable to each of the contexts described above, e.g. a guide to the type of detail needed in an AEFI report or the breadth of investigation that might be warranted in case assessment or cluster investigation. Of note, the same or similar mechanisms may apply to more than one of the AEFI cause-specific definitions and this is reflected in the lists below.

A. Vaccine product-related & Vaccine quality defect-related reactions

Underlying mechanisms could be the same whether or not the reaction is due to an inherent property of the vaccine or a quality defect in manufacture. Thus, mechanisms for product-related reactions and quality defect-related reactions are combined into a single category in this section and include but are not limited to the list provided in this report.

Vaccines are designed to induce a response by the immune system which involves a complex interaction between the vaccine antigens, the adjuvant (if present), antigen-presenting cells, lymphocytes and multiple immune mediators (cytokines). This interaction is important to the development of the desired immunity against the specific vaccine-preventable disease. However, the immune response in a vaccinee may manifest as relatively common and mild adverse reactions to the vaccine(s), such as injection site redness and swelling or fever. Homeostatic mechanisms usually limit the inflammatory response, so that such reactions are short-lived and

have no lasting consequence. Uncommonly, the immune response to one or more vaccine components may result in a longer-lasting and more severe adverse reaction. Rarely, the immune response may cause a life-threatening allergic reaction. Possible mechanisms for immune-mediated vaccine reactions are listed in Section 3.3.4 (2).

It is important to note that vaccine product-related reactions may unmask a predisposition to other adverse events in certain high-risk individuals that would not occur in the majority of vaccinees. For example, fever is a relatively common inflammatory response following vaccination. For most vaccinees the fever is of short duration and there are no associated adverse reactions. However, in children with an underlying seizure disorder, or in infants and toddlers with a tendency to have febrile seizures the fever may trigger a seizure. Other events that cause fever, like respiratory infection, could also trigger a seizure. In such cases, the seizures result as a combination of an inherent property of the vaccine that caused fever and underlying factors in the vaccinee that lowered the threshold for seizure associated with fever.

(1) Reaction associated with the route and/or site of administration of the vaccine product or vaccinee-specific characteristics:

   a. Bell's palsy following intranasal administration of a specific influenza vaccine where the causative mechanism was attributed to the vaccine composition combined with the mode of administration (*32*).
   b. Pain at the time of injection and associated physiologic responses.

(2) Immune-mediated vaccine reactions:

   a. Local reaction, with involvement of injection site, due to one or more vaccine components
      (i) Non-granulomatous inflammation with or without regional lymphadenitis

         1. Extensive limb swelling e.g. post-DTP vaccination *(33, 34, 35)*
         2. Mild, moderate or severe local inflammation, manifest as one or more of swelling, redness, pain, local tenderness and induration. Examples of the mechanisms underlying more severe reactions include:
            – subcutaneous injection of a vaccine (e.g. alum adsorbed) recommended for intramuscular administration

- localized antigen-antibody reaction (antibody excess)
- aluminium adjuvant hypersensitivity, or
- infection

(ii) Granulomatous inflammation at the injection site with or without regional lymphadenitis (most commonly related to BCG vaccine).

b. Multisystem (generalized) reaction due to one or more vaccine components
   (i) Systemic inflammatory response, e.g. fever or lethargy
   (ii) Mast cell degranulation
      1. IgE mediated hypersensitivity (anaphylaxis)
      2. Non-IgE mediated hypersensitivity (reactions in this group are commonly referred to as anaphylactoid reactions[1])
   (iii) Disseminated granulomatous reaction, e.g. disseminated BCG in immunodeficient hosts
   (iv) Immune complex mediated reaction (Serum Sickness Reaction).

c. Organ-specific reaction due to one or more vaccine components
   (i) Auto-immune or undefined mechanism
      1. CNS e.g. demyelinating conditions such as GBS post-influenza vaccination (*36*)
      2. Blood e.g. thrombocytopenia post-MMR vaccination
      3. Skin e.g. rashes after vaccination, including urticaria.[2]

(3) Consequence of replication of vaccine-associated microbial agent(s) in the vaccinee or a close contact of the vaccinee. The microbial agent(s) could be:

a. Attenuated vaccine agent.
b. Wild type vaccine agent due to insufficient inactivation during the manufacturing process.

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[1] Anaphylactoid reactions are clinically indistinguishable from anaphylaxis. The clinical symptoms of anaphylaxis are due to mast cell degranulation and the same mechanism underlies non-IgE mediated hypersensitivity. In the latter, mast cell degranulation may occur due to IgG mediated, complement-mediated or undefined mechanisms. Sometimes further testing for IgE antibodies to vaccine components can differentiate these two mechanisms.

[2] Rashes are frequently urticarial, sometimes with a poorly understood but presumed immune mechanism. It is important to note that rashes following immunization may be multifactorial, resulting from local inflammation, mast cell degranulation or replication of live agents (e.g. measles rash post-MMR vaccine, varicella rash post-varicella zoster virus vaccine). Rashes may also be localised or generalized.

c. Contaminant introduced into vaccine during the manufacturing process.

(4) Direct toxic effect of vaccine component or contaminant (e.g. quality defect).

B. Immunization error-related reaction

Since the emphasis for AEFIs falling in this category is on their preventable nature, the mechanisms focus on the nature of the error rather than on the biologic process(es) giving rise to the specific AEFI(s). Still, many of the AEFIs in this category B result from the same or similar processes underlying vaccine product-related or vaccine quality defect-related reactions (category A). Thus, where appropriate, a cross reference to the relevant mechanism(s) from category A is shown in brackets below.

For example, when an individual has a documented hypersensitivity to one or more components of a vaccine but a vaccine provider fails to adhere to what is a known contraindication, the resulting anaphylaxis is due to an error in vaccine prescribing (category B.(2)a.(i)) and thus could have been prevented. At the same time the anaphylaxis episode is also an IgE mediated hypersensitivity reaction as described in category A.(2)b.(ii) above.

(1) Error in vaccine handling:

a. Exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the vaccine (and its diluent where applicable)
   (i) Failure to vaccinate as a result of inactivation of the active vaccine components
   (ii) Systemic or local reactions due to changes in the physical nature of the vaccine such as agglutination of aluminium-based excipients in freeze-sensitive vaccines.

b. Use of a product after the expiry date
   (i) Failure to vaccinate as a result of loss of potency or non-viability of an attenuated product.

(2) Error in vaccine prescribing or non-adherence to recommendations for use:

a. Failure to adhere to a contraindication
   (i) Anaphylaxis following administration of a vaccine to an individual known to have an immune-mediated hypersensitivity to one or more components (category A.(2)b.(ii))

(ii) Disseminated infection with an attenuated live vaccine agent following administration to an individual with a known immunodeficiency that contraindicated use of any live vaccines (category A.(3)a)

(iii) Vaccine-associated paralytic polio in an immunocompromised household contact of a child given oral polio vaccine (category A.(3)a).

b. Failure to consider appropriately warnings or precautions for vaccine use.

c. Failure to adhere to vaccine indications or prescription (dose or schedule).

(i) Systemic and/or local reactions following administration of incorrect dose

(ii) Systemic and/or local reactions following administration of wrong product or administration to an individual in an incorrect age group

(iii) Vaccine failure if a live attenuated product is given too soon after blood products or at an age when maternally transferred antibody could interfere with replication required to induce an immune response

(iv) Neurologic, muscular, vascular or bony injury due to incorrect injection site, equipment or technique.

(3) Error in administration:

a. Use of an incorrect diluent or injection of a product other than the intended vaccine

(i) Failure to vaccinate due to incorrect diluent

(ii) Reaction due to the inherent properties of whatever was administered other than the intended vaccine or diluent.

b. Incorrect sterile technique or inappropriate procedure with a multidose vial

(i) Infection at the site of injection due to a microbial contaminant introduced during administration of the vaccine

(ii) Infection beyond the site of injection due to a microbial contaminant introduced during administration of the vaccine.

c. Failure to ensure a safe environment during and immediately following immunization

(i) Head injury during a syncopal episode post-immunization (categories C.(1-3) below).

d. Inadvertent administration of vaccine to someone for whom it was not intended, e.g. via a needlestick injury or splash to the eye (categories A.(1)-(4) depending on the vaccinee characteristics).

C. Immunization anxiety-related reaction

The types of reactions caused by immunization anxiety include but are not limited to:

(1) Vasovagal mediated reactions

(2) Hyperventilation mediated reactions

(3) Stress-related psychiatric disorders

D. Coincidental event

AEFIs can result from underlying or emerging conditions of the vaccinee as well as external exposures that can cause harm independent of immunization. These include but are not limited to:

(1) Underlying or emerging condition(s) in the vaccinee:

a. Manifestation or complication of a congenital or inherited underlying disease condition or birth injury.
b. Manifestation or complication of an underlying acquired disease condition that may or may not have been diagnosed prior to immunization.
c. Psychogenic illness.

(2) Conditions caused by exposure to something other than vaccine:

a. Infection due to agents such as bacteria, viruses, fungi or parasites.
b. Adverse reaction due to recent or concomitant medication or use of illicit substances.
c. Allergic and other hypersensitivity reactions due to exposure to allergens other than those present in the vaccine.[1]
d. Injury due to exposure to environmental toxins.
e. Injury due to trauma including surgery.

[1] This mechanism would include for example, a latex-sensitive individual who develops a hypersensitivity reaction to latex gloves worn by the vaccinator.

3.4 Points to consider regarding differences between vaccines and drugs in signal[1] detection (*1*)

With respect to signal detection, there is substantial overlap of vaccines and drugs in the methods and approaches used. Nonetheless, vaccines present some important differences worthy of special attention. This brief report presents points to consider for persons undertaking signal detection for vaccines.

The development of vaccines and their settings of post-licensure use lead to several special issues. In general, vaccine pre-licensure trials are substantially larger than those for drugs and consequently are powered to detect rarer adverse events.

3.4.1 Universal immunization and public communication of safety signals

The goal of ensuring the safety of vaccines leads to the institution of rigorous signal detection efforts. Vaccines are often required by authorities for public health purposes, school attendance or other reasons, resulting in greater than 90% coverage rates; this is sometimes called "universal immunization". Universal immunization programmes have successfully controlled or eliminated multiple infectious diseases. However, certain publicized AEFIs based on weak scientific data have led to concerns followed by substantial decreases in vaccination coverage rates and subsequent increases in incidence of vaccine-preventable disease (*37*). The lack of an alternative vaccine can exacerbate such situations. Consequently, the public communication of unconfirmed vaccine safety signals ought to take into account potential effects on vaccination coverage as well as benefits (e.g. adverse event case ascertainment) and any other risks of communicating the signal.

3.4.2 Implications of specific ages at vaccination

Paediatric vaccines are often recommended to be administered at specific ages, predominantly to healthy infants and children. Multiple diseases and conditions have characteristic ages at onset that may occur contemporaneously, or nearly so, with recommended vaccinations. Even in the

[1] The definition of a signal by the CIOMS Working Group VIII was adopted for this report, where a signal was defined as "information that arises from one or multiple sources (including observations and experiments) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action" (*1*).

absence of a causal association of a vaccination with a disease, a temporal association may be observed. For example, if a disease's median age of onset and diagnosis occurred at age 15 months, and if the disease were not causally associated with a vaccination recommended at age 15 months, one would nonetheless at a minimum expect spontaneous reports of that disease in temporal association with vaccination. Some investigators or members of the public might then posit a causal association even though none exists. On the other hand, contemporaneous occurrence of the recommended age of vaccination and the natural onset of disease does not by itself rule out a causal association or a triggering effect, and further investigation may be warranted depending on the totality of the available information.

3.4.3 Settings of vaccine administration

Vaccine administration settings may differ from those for drugs – examples of such vaccination settings, where physicians are often absent, include public settings such as vaccination clinics, pharmacies and schools. Consequently, the nature of adverse event reports following vaccination in these settings may differ in both quantity and quality from the settings where drugs traditionally are administered or prescribed. For example, in mass vaccination campaigns there may be clusters of vasovagal-like episodes, some involving syncope, that may be mistakenly reported as other, more severe conditions without medical confirmation (*38*). In contrast, a new serious adverse event may first come to attention during a mass vaccination campaign as occurred in 1976 with GBS following swine flu vaccine use in the US (*39*).

3.4.4 Live attenuated viral or bacterial vaccines

In clear contrast to drugs, some vaccines are composed of attenuated viruses or bacteria that are intended to cause mild infections that induce protective immunity. Rarely these vaccine-induced infections result in serious disease. Investigation of such infections is important. Identification of the pathogenic organism, and determining whether it is vaccine strain or "wild type" through culture, DNA-based techniques or other methods can be crucial to linking the vaccine to the adverse event.

3.4.5 Vaccine components included for antigenic or non-antigenic attributes

Antigens in vaccines are intended to elicit a protective immune response in the vaccinee. However, there exists the possibility that vaccination may inadvertently elicit an unintended and pathologic immune or

autoimmune response (e.g. immune thrombocytopenic purpura following MMR vaccination). In addition, components of vaccines that are included for attributes other than their antigenic value such as adjuvants intended to augment the immune response to vaccine antigens or preservatives intended to prevent bacterial contamination of multi-dose vials may lead to adverse events distinct from those typically associated with drugs. In addition, these components may be present in different vaccines protecting against widely varying diseases, and this potential should be taken into account in data analyses.

3.4.6 Combination vaccines and simultaneous administration of multiple vaccines

Vaccines are not only formulated in fixed combinations (e.g. diphtheria-tetanus-pertussis (DTP) vaccine) but also multiple vaccines are frequently administered simultaneously at different body sites. Consequently in situations where one vaccine is associated with an adverse event, it may be difficult to determine which of multiple simultaneously administered vaccines underlies the association. Depending on the analytic approach, a co-administered vaccine may be spuriously associated with an adverse event (for example, using automated signal detection approaches, DTP vaccine may be found to be associated with polio, although the disease was due to co-administered oral polio vaccine (OPV)).

3.4.7 Data analytic issues

Both regulatory authorities and vaccine manufacturers maintain spontaneous adverse event report databases, which vary in size, diversity of products, case characteristics and countries covered. Spontaneous adverse event report databases may include vaccines only (such as VAERS) or both vaccines and drugs (such as the European Union's EudraVigilance). Depending on the type of signal detection task and approach used, as well as the scientific question being asked, one of these two types of databases may perform better than the other. In a vaccines-only database, particularly in manufacturers' databases, one vaccine may compose a relatively large proportion of the adverse event reports and might skew the analyses. In a mixed drugs-vaccines database, drug reports will usually greatly outnumber vaccine reports, and analyses should take this into account where appropriate. Some of the common differences between groups receiving vaccines and drugs are mentioned in this annex. In the US databases there are also substantial differences in the proportion of vaccine and drug reports that are categorized as serious, about 15% for vaccines and substantially

more for drugs (the percentage for drugs may decrease with the widespread implementation of electronic submission). Combining such disparate databases for analysis clearly may be problematic and should be done carefully, taking into account the potential for bias and confounding. Another aspect that differs between vaccines and drugs that may affect signal detection and analyses is the substantially greater number of drugs than vaccines. In addition, in the US, a much greater proportion of adverse event reports from manufacturers is found in the US Adverse Event Reporting System (AERS) than VAERS. This may result in greater differences in signal detection between manufacturer databases and VAERS than between manufacturer databases and AERS; analogous situations may exist in other countries or settings. In addition, depending on a report's source, its quality and the potential for obtaining additional follow-up information for assessment of signals may vary.

Additional analytic issues for consideration include: in the setting of universal immunization, signal detection and assessment modalities that utilize unvaccinated persons as a comparison group should take into account the possibility that unvaccinated persons, who may be a small minority, differ systematically from vaccinated persons in ways that may be associated with the adverse event of interest. This potential for confounding should be explicitly addressed. In addition, confounding by indication is a greater concern in drug signal detection than for vaccines, because in general vaccinees are healthier than those who receive drugs. Moreover, vaccines are often used in paediatric populations, whereas drugs are usually used in older people. These differences may affect choice of appropriate comparison groups and analytic approaches.

In any vaccine adverse event analysis, confounders or sources of bias to be considered include (but are not limited to) age, gender, race/ethnicity, season (e.g. for influenza vaccines), calendar time and country/region; in addition, it is usually desirable to take event seriousness into account.

3.4.8 Possible analyses by class, brand or lot

Whether to analyse vaccines of the same type together and/or separately is an important decision. For example, in a given annual influenza season, an association between GBS and influenza vaccine may be signalled by analyses of all inactivated influenza vaccines combined and/or of each brand of vaccine independently. In addition, analysis by vaccine lot is possible and may be indicated for routine surveillance or in the event of a potential cluster or other lot safety concern.

3.4.9 Small number of doses per vaccine per person

Specific vaccines are usually administered to an individual in a series of a small number of doses (rarely more than four times annually and most often fewer). In contrast, many drugs are administered at least daily, often for extended duration. Vaccines' infrequent dosing schedule and induction of long-term immunity make dechallenge, useful for drug safety assessment, generally not applicable for vaccines; similarly, opportunities for rechallenge are much less frequent for vaccines than for drugs. Safety analyses involving vaccines may need to take into account these differences. Self-control methodologies, in which an individual who has received a product has "exposed" and "unexposed" time windows whose adverse event incidence rates are compared, have particular advantages in hypothesis testing, signal evaluation and possibly in detection as well (*40, 41*). For drugs administered frequently, "unexposed" time windows after drug initiation appropriate for analysis may be less available.

3.4.10 Automated signal detection

Automated signal detection (sometimes called "data mining") is increasingly used and has some specific considerations in addition to the ones noted above (*42, 43*). In databases that include both drug and vaccine adverse event reports, investigators should give careful consideration to the choice of the comparison group. For example, a comparison group including drugs may result in the detection of vaccine adverse event signals that relate to vaccines as a class (e.g. fever) and may also identify false signals (e.g. sudden infant death syndrome) or already known mild and expected reactions linked to vaccination (e.g. local injection site reactions). However, simply restricting analyses to vaccines does not solve all problems, and issues highlighted in the section *Data Analytic Issues* and other sections of the CIOMS VIII report *(1*) – such as addressing potential confounding by age, simultaneous administration of multiple vaccines, and other factors – should be taken into account. It may be appropriate to undertake automated signal detection using some analyses of vaccines alone and other analyses including drugs too.

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4

Brighton Collaboration case definitions and guidelines

Officially launched in 2000, the Brighton Collaboration is "an international voluntary collaboration to facilitate the development, evaluation, and dissemination of high quality information about the safety of human vaccines" (https://brightoncollaboration.org/public). Its initial focus has been the development of standardized case definitions of AEFIs to facilitate collection and comparison of data from clinical trials, epidemiological studies and surveillance systems. A common understanding of AEFIs across regions and in different settings is critical to effective vaccine pharmacovigilance. Brighton Collaboration working groups develop and finalize case definitions, which have been published in the journal *Vaccine* and on the Brighton Collaboration website. Brighton Collaboration case definitions are designed to identify cases and determine their diagnostic certainty, not for the primary purpose of causality assessment or patient management. They are typically structured with multiple levels of diagnostic certainty, and include a preamble with justification for decisions made by the Brighton Collaboration working group for the specific case definition, as well as guidelines for use of the case definition. Draft case definitions are evaluated and validated by a reference group prior to finalization. Following publication, the case definitions undergo further evaluation and implementation in multiple settings, with regular review and revision as necessary.

One of the activities of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance during 2005 to 2010 was to review and endorse the Brighton Collaboration case definitions. Case definitions that were already published at the time this Working Group was established were reviewed, with comments on limitations and the need for revision as appropriate, and subsequently endorsed. Final drafts of new, unpublished case definitions were reviewed, modified as appropriate, and endorsed by this Working Group. Endorsement by the Working Group was acknowledged in the published case definitions. The review and endorsement process by this Working Group, including interactions with the Brighton Collaboration, is described in Annex 4. In addition to final review and endorsement, members of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance were encouraged to contribute to Brighton Collaboration working or reference groups.

Since multiple regions (industrialized and non-industrialized countries) and stakeholders in vaccination (regulatory, industry, public health, academia) were represented on the CIOMS/WHO Working Group, it is expected that review by the Working Group has resulted in improvement in the quality of the case definitions. As well, the anticipation is that their use by a variety of stakeholders across multiple settings will be enhanced.

4.1 AEFI-specific case definitions

In order to provide a quick reference to the Brighton Collaboration case definitions, all case definitions endorsed by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance at the time of preparation of this Working Group report are reproduced in this section of the report; only the core case definitions are reproduced, however, the Working Group emphasizes that each published case definition comprises a more comprehensive document which includes a preamble, the core case definition and guidelines for data collection, analysis and presentation relevant to the specific definition. The complete case definitions are accessible through the Brighton Collaboration website and journal references provided in this report (see also Section 5.).

The most up-to-date and complete case definitions (i.e. preamble, core case definition, and guidelines for data collection, analysis and presentation) should always be accessed on the Brighton Collaboration website and referenced accordingly (https://brightoncollaboration.org/public).

The case definitions below are listed in alphabetical order, with the case definitions for (a) injection site reactions, and (b) vaccinia-related adverse events grouped at the end of the list.[1]

Among these case definitions endorsed by the Working Group, the group developed abridged versions of a sample of five case definitions, including a common brief introduction (see Annex 5) and a summary preamble with each respective core definition for translation into French and Portuguese: *Abscess at injection site*; *Aseptic meningitis*, *Cellulitis at injection site*; *Encephalitis, myelitis, and acute disseminated encephalomyelitis*; and *HHE*. The scope of translation supported by the Working Group is further discussed in Section 5.1. The five summarized and translated case definitions are also available through the Brighton Collaboration website (https://brightoncollaboration.org/public).

4.1.1 Acute intussusception in infants and young children (1)

Intussusception is the invagination of one segment of intestine into a segment of distal intestine.

[1] The case definitions were published at different time points. In this report efforts have been made, supported by the Brighton Collaboration, to present the core definitions in a standardized format.

Level 1 of Diagnostic Certainty

Surgical criteria:

- The demonstration of invagination of the intestine at surgery;

AND/OR

Radiologic criteria:

- The demonstration of invagination of the intestine by either air or liquid contrast enema; *OR*
- The demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features[a] that is proven to be *reduced* by hydrostatic enema on *postreduction ultrasound*;

AND/OR

Autopsy criteria:

- The demonstration of invagination of the intestine.

Level 2 of Diagnostic Certainty

Clinical criteria:

- Two major criteria (see major and minor criteria for diagnosis below);

OR

- One major criterion[b] and three minor criteria (see major and minor criteria for diagnosis below).

Level 3 of Diagnostic Certainty

Clinical criteria:

- Four or more minor criteria (see minor criteria for diagnosis below).

Any Level of Diagnostic Certainty

In the absence of surgical criteria with the definitive demonstration of an alternative cause of bowel obstruction or intestinal infarction at surgery (e.g. volvulus or congenital pyloric stenosis).

Major and minor criteria used in the case definition for the diagnosis of intussusception

Major criteria

1. *Evidence of intestinal obstruction:*	I. History of bile-stained vomiting; *and either* II. Examination findings of acute abdominal distension and abnormal or absent bowel sounds; *or* III. Plain abdominal radiograph showing fluid levels *and* dilated bowel loops.
2. *Features of intestinal invagination:*	One or more of the following: I. abdominal mass; II. rectal mass; III. intestinal prolapse; IV. plain abdominal radiograph showing a visible intussusceptum or soft tissue mass; V. abdominal ultrasound showing a visible intussusceptum or soft tissue mass; VI. abdominal CT scan showing a visible intussusceptum or soft tissue mass.
3. *Evidence of intestinal vascular compromise or venous congestion:*	I. Passage of blood per rectum; *or* II. Passage of a stool containing "red currant jelly" material; *or* III. Blood detected on rectal examination.

Minor criteria

- Predisposing factors: age <1 year and male sex;
- Abdominal pain;
- Vomiting;[c]
- Lethargy;[d]
- Pallor;[d]
- Hypovolemic shock;
- Plain abdominal radiograph showing an abnormal but non-specific bowel gas pattern.

Notes for acute intussusception case definition

a. Target sign or doughnut sign on transverse section *and* a pseudo-kidney or sandwich sign on longitudinal section.

b. If one major criterion is the passage of blood per rectum that is mixed in a diarrheal stool, consideration should be given to infectious causes (e.g. *E. coli*, shigella, or amoebiasis). In such cases two major criteria should be met.

c. If the vomiting is bile-stained, it cannot be counted twice as a major and minor criterion.

d. Lethargy and pallor typically occur intermittently in association with acute spasms of abdominal pain. In patients with severe or prolonged intussusception, lethargy and pallor may become a constant feature associated with a deterioration in cardiovascular status and impending hypovolemic shock.

4.1.2 Anaphylaxis (2)

For all levels of diagnostic certainty

Anaphylaxis is a clinical syndrome characterized by

- sudden onset *AND*
- rapid progression of signs and symptoms *AND*
- involving multiple (≥2) organ systems, as follows.

Level 1 of diagnostic certainty

- ≥1 major dermatological *AND*
- ≥1 major cardiovascular *AND/OR* ≥1 major respiratory criterion.

Level 2 of diagnostic certainty

- ≥1 major cardiovascular *AND* ≥1 major respiratory criterion *OR*
- ≥1 major cardiovascular *OR* respiratory criterion *AND*
- ≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems) *OR*
- (≥1 major dermatologic) *AND* (≥1 minor cardiovascular *AND/OR* minor respiratory criterion).

Level 3 of diagnostic certainty

- ≥1 minor cardiovascular *OR* respiratory criterion *AND*
- ≥1 minor criterion from each of ≥2 different systems/categories.

The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

Major and minor criteria used in the case definition of anaphylaxis

Major criteria

Dermatologic or mucosal	• generalized urticaria (hives) or generalized erythema • angioedema*, localized or generalized • generalized pruritus with skin rash
Cardiovascular	• measured hypotension • clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: – tachycardia – capillary refill time >3 s – reduced central pulse volume – decreased level of consciousness or loss of consciousness
Respiratory	• bilateral wheeze (bronchospasm) • stridor • upper airway swelling (lip, tongue, throat, uvula, or larynx) • respiratory distress – 2 or more of the following: – tachypnoea – increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.) – recession – cyanosis – grunting

* Not hereditary angioedema.

Minor criteria

Dermatologic or mucosal	• generalized pruritus without skin rash • generalized prickle sensation • localized injection site urticaria • red and itchy eyes
Cardiovascular	• reduced peripheral circulation as indicated by the combination of at least 2 of: – tachycardia and – a capillary refill time of >3 s without hypotension – a decreased level of consciousness
Respiratory	• persistent dry cough • hoarse voice • difficulty breathing without wheeze or stridor • sensation of throat closure • sneezing, rhinorrhea
Gastrointestinal	• diarrhoea • abdominal pain • nausea • vomiting
Laboratory	• Mast cell tryptase elevation > upper normal limit

4.1.3 Aseptic meningitis (3)

Level 1 of diagnostic certainty

- Clinical evidence of acute meningitis such as fever, headache, vomiting, bulging fontanelle, nuchal rigidity or other signs of meningeal irritation,

AND

- Pleocytosis in CSF[a] determined as:
  – >5 leukocytes/mm^3 (μL) if patient is 2 months of age[b] or older,
  – >15 leukocytes/mm^3 (μL) in infants younger than 2 months,[b]

AND

- Absence of any microorganism on Gram stain of CSF,

AND

- Negative routine bacterial culture of CSF in the absence of antibiotic treatment before obtaining the first CSF sample.

Level 2 of diagnostic certainty

- Clinical evidence of acute meningitis such as fever, headache, vomiting, bulging fontanelle, nuchal rigidity or other signs of meningeal irritation,

AND

- Pleocytosis in CSF[a] determined as:
  - >5 leukocytes/mm^3 (μL) if patient is 2 months of age[b] or older,
  - >15 leukocytes/mm^3 (μL) in infants younger than 2 months,[b]

AND

- Absence of any microorganism on Gram stain of CSF,

AND

- No bacterial culture of CSF obtained, OR negative culture in the presence of antibiotic treatment before obtaining the first CSF sample.

Level 3 of diagnostic certainty

Not applicable.

If the case meets criteria for aseptic meningitis and encephalitis case definition (*4*), it should be reported only as encephalitis.

Notes for aseptic meningitis case definition

a. In presumed traumatic lumbar puncture (i.e. erythrocytes in the CSF without other known cause such as head trauma, haemorrhagic stroke, or necrotizing encephalitis), CSF pleocytosis is defined as a >1:1 ratio of observed and predicted leukocytes in CSF. Predicted CSF leukocytes are calculated by using the formula: predicted CSF leukocytes = CSF erythrocytes × (blood leukocytes/blood erythrocytes). In the absence of data on blood erythrocytes and leukocytes, pleocytosis can be defined as a >1:500 ratio of CSF leukocytes and CSF erythrocytes.

b. Chronological age (birth date).

4.1.4 Diarrhea[a] (5)

Level 1 of diagnostic certainty

Diarrhea is defined as:

- An increase by 3 or more bowel movements (above normal or baseline) occurring within a 24-h period[b, c]

AND

- A runny or liquid consistency of these stools.[d, e, f]

Level 2 of diagnostic certainty

Diarrhea is defined as:

- An increase in frequency of bowel movements (above normal or baseline)[c, g]

AND

- A runny or liquid consistency of these stools.[d, e, f]

Notes for diarrhea case definition

Note: Refer to the full document for the guidelines and appendices mentioned in notes below.

a. This definition does not attempt to establish a causal link between immunization and diarrhea. Assessing causality requires a range of complex factors that are independent from establishing the presence of diarrhea as a clinical entity.

b. Any 24-h period e.g. Wednesday 6:00 hours to next day Thursday at 6:00 hours.

c. Normal bowel habits are the baseline bowel habits of that person and may vary depending on age, type of feeding (in infants) and dietary factors.

d. Diarrhea may have blood or mucus in the stools and can occur with or without dehydration.

e. Grading the severity of diarrhea is further described in Appendix A.

f. For example, to meet the case definition, a person who normally has three bowel movements per day would need to have an increase to 6 bowel movements per day that are looser than normal.

g. Diarrhea is described without specification of numbers for frequency or time.

4.1.5 Encephalitis, myelitis and acute disseminated encephalomyelitis

(ADEM)[a] (6)

A. Encephalitis

Level 1 of diagnostic certainty:[b] Encephalitis

(a) Demonstration of acute inflammation of central nervous system parenchyma (+/– meninges) by histopathology.

Level 2 of diagnostic certainty:[c,d] Encephalitis

(a) Encephalopathy (e.g. depressed or altered level of consciousness, lethargy, or personality change lasting >24 hours),

AND INCLUDING

(b) **ONE OR MORE** of the following:
   1. Decreased or absent response to environment, as defined by response to loud noise or painful stimuli,
   2. Decreased or absent eye contact,
   3. Inconsistent or absent response to external stimuli,
   4. Decreased arousability,
   5. Seizure associated with loss of consciousness (*7*).

OR

(c) Focal or multifocal findings referable to the central nervous system, including one or more of the following:
   1. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness),
   2. Cranial nerve abnormality/abnormalities,[e]
   3. Visual field defect/defect(s),
   4. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
   5. Motor weakness (either diffuse or focal; more often focal)[e]
   6. Sensory abnormalities (either positive or negative; sensory level),
   7. Altered deep tendon reflexes (hypo- or hyperreflexia, reflex asymmetry),
   8. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.

AND (for both possibilities to reach Level 2)

(a) **TWO OR MORE**[f] of the following indicators of inflammation of the CNS:
   1. Fever (temperature >38ºC),
   2. CSF pleocytosis (>5 WBC/mm^3 in children >2 months of age; >15 WBC/mm^3 in children <2 months of age),
   3. EEG findings consistent with encephalitis,[g] or
   4. Neuroimaging consistent with encephalitis.[h]

Level 3 of diagnostic certainty:[c,d] Encephalitis

(a) Encephalopathy (e.g. depressed or altered level of consciousness, lethargy, or personality change lasting >24 hours),

AND INCLUDING

(b) **ONE OR MORE** of the following:
   1. Decreased or absent response to environment, as defined by response to loud noise or painful stimuli,
   2. Decreased or absent eye contact,
   3. Inconsistent or absent response to external stimuli,
   4. Decreased arousability, or
   5. Seizure associated with loss of consciousness (*7*).

OR

(c) Focal or multifocal findings referable to the central nervous system, including **one or more** of the following:
   1. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness),
   2. Cranial nerve abnormality/abnormalities[e]
   3. Visual field defect/defect(s),
   4. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
   5. Motor weakness (either diffuse or focal; more often focal)[e]
   6. Sensory abnormalities (either positive or negative; sensory level),
   7. Altered deep tendon reflexes (hypo- or hyperreflexia, reflex asymmetry), or
   8. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.

AND (for both possibilities to reach Level 3)

(d) **ONE**[f] of the following indicators of inflammation of CNS:
   1. Fever (temperature >38ºC),
   2. CSF pleocytosis (>5 WBC/mm^3 in children >2 months of age; >15 WBC/mm^3 in children <2 months of age),
   3. EEG findings consistent with encephalitis,[g] or
   4. Neuroimaging consistent with encephalitis.[h]

Level 3A of diagnostic certainty[e,i]

(a) Insufficient information is available to distinguish case between acute encephalitis or ADEM; case unable to be definitively classified.

Exclusion criterion for levels 2 and 3 of diagnostic certainty

(a) Other diagnosis for illness present.[j]

B. Myelitis

Level 1 of diagnostic certainty: Myelitis

(a) Demonstration of acute spinal cord inflammation (+/– meninges) by histopathology,

Level 2 of diagnostic certainty:[k] Myelitis

(a) Myelopathy (development of sensory, motor, or autonomic dysfunction attributable to the spinal cord, including upper- and/or lower-motor neuron weakness, sensory level, bowel and/or bladder dysfunction, erectile dysfunction),

AND

(a) **TWO OR MORE**[l] of the following indicators suggestive of spinal cord inflammation:
   1. Fever (temperature >38ºC),
   2. CSF pleocytosis (>5 WBC/mm^3 in children >2 months of age; >15 WBC/mm^3 in children <2 months of age),
   3. Neuroimaging findings demonstrating acute inflammation (+/– meninges), or demyelination of the spinal cord.

Level 3 of diagnostic certainty:[k] Myelitis

(a) Myelopathy (development of sensory, motor, or autonomic dysfunction attributable to the spinal cord, including upper- and/or lower-motor neuron weakness, sensory level, bowel and/or bladder dysfunction, erectile dysfunction),

AND

(a) **ONE**[l] of the following indicators suggestive of spinal cord inflammation:
   1. Fever (temperature >38ºC),
   2. CSF pleocytosis (>5 WBC/mm^3 in children >2 months of age; >15 WBC/mm^3 in children <2 months of age),
   3. Neuroimaging findings demonstrating acute inflammation (+/– meninges), or demyelination of the spinal cord.

Exclusion criterion for levels 2 and 3 of diagnostic certainty

(a) Other diagnosis for illness present[j]

Cases fulfilling the criteria for both encephalitis and myelitis in any category would be classified as *encephalomyelitis*.

C. ADEM

Level 1 of diagnostic certainty:[m] ADEM

(a) Demonstration of diffuse or multifocal areas of demyelination by histopathology.

OR

(b) Focal or multifocal findings referable to the central nervous system, including **one or more** of the following:
   1. Encephalopathy (see case definition for encephalitis for specification of encephalopathy),
   2. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness),
   3. Cranial nerve abnormality/abnormalities,
   4. Visual field defect/defects,
   5. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
   6. Motor weakness (either diffuse or focal; more often focal),
   7. Sensory abnormalities (either positive or negative; sensory level),
   8. Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes), or
   9. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus,

AND

(c) Magnetic resonance imaging (MRI) findings displaying diffuse or multifocal white matter lesions on T2-weighted, diffusion-weighted (DWI), or fluid-attenuated inversion recovery (FLAIR) sequences (+/– gadolinium enhancement on T1 sequences),

AND

(d) Monophasic pattern to illness (i.e. absence of relapse within a *minimum* of 3 months of symptomatic nadir)[n,o,p].

Level 2 of diagnostic certainty:[c,q] ADEM

(a) Focal or multifocal findings referable to the central nervous system, including one or more of the following:
   10. Encephalopathy (see case definition for encephalitis for specification of encephalopathy),
   11. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness),

12. Cranial nerve abnormality/abnormalities,
13. Visual field defect/defects,
14. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
15. Motor weakness (either diffuse or focal; more often focal),
16. Sensory abnormalities (either positive or negative; sensory level),
17. Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes), or
18. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus,

AND

(b) Magnetic resonance imaging (MRI) findings displaying diffuse or multifocal white matter lesions on T2-weighted, diffusion-weighted (DWI), or fluid-attenuated inversion recovery (FLAIR) sequences (+/– gadolinium enhancement on T1 sequences),

AND

(c) Insufficient follow-up time achieved to document absence of relapse within a minimum period of 3 months following symptomatic nadir[n,o,p].

Level 3 of diagnostic certainty:[c] ADEM

(a) Focal or multifocal findings referable to the central nervous system, including one or more of the following:
19. Encephalopathy (see case definition for encephalitis for specification of encephalopathy),
20. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness),
21. Cranial nerve abnormality/abnormalities,
22. Visual field defect/defects,
23. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
24. Motor weakness (either diffuse or focal; more often focal),
25. Sensory abnormalities (either positive or negative; sensory level),
26. Altered deep tendon reflexes (hypo- or hyperreflexia, asymmetry of reflexes), or
27. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.

Level 3A[e,i]

- Insufficient information is available to distinguish case between acute encephalitis or ADEM; case unable to be definitively classified.

Exclusion criteria for all levels of diagnostic certainty

- Presence of a clear alternative acute infectious or other diagnosis for illness,
- Recurrence or relapse of illness at any point following a 3-month period of clinical improvement from symptomatic nadir, or
- If known, MRI findings or histopathologic data inconsistent with the diagnosis of ADEM.

Notes for encephalitis, myelitis and ADEM case definitions

a. If the lowest applicable level of diagnostic certainty of the definition for a definitive category (i.e. Level 3, excluding Level 3A) is met and there is evidence that the criteria of the next higher level of diagnostic certainty (Level 2) are met, the event should be classified in the next category. This approach should be continued until the highest level of diagnostic certainty for a given event can be determined. Thus, if a case fits diagnostic criteria for both categories (encephalitis and ADEM), but reaches a higher level of diagnostic certainty in one, the higher level supercedes, and the case should be classified according to the category in which the higher diagnostic certainty level is reached. The Working Group recognizes that under this paradigm, it is possible to reach a higher level of diagnostic certainty for ADEM with less stringent criteria than it is for encephalitis e.g. Level 1 diagnostic certainty for encephalitis requires histopathologic diagnosis, whilst ADEM Level 1 does not require this. However, in the absence of a biological marker, the diagnosis of ADEM rests upon the proper neuroimaging findings in the appropriate clinical context, and the combination of appropriate neuroimaging and a monophasic pattern of illness are as close to a gold standard as exist for this clinical entity. Thus, one may have a higher level of diagnostic certainty of ADEM than of encephalitis, in the absence of other biologic data. When Level 1 ADEM and Level 2 encephalitis, or Level 2 ADEM and Level 3 encephalitis are met, the best category to choose would be ADEM.

b. The encephalitis/ADEM Working Group recognizes that, in most cases, histopathologic examination of tissue will not be practicable as a method of diagnosis; this may particularly be the case in developing countries. However, histopathologic demonstration of cerebral inflammation remains the "gold standard" for the diagnosis of encephalitis, and as such, the group has determined that this should be Level 1 for determination of encephalitis.

c. Levels 2 and 3 of diagnostic certainty have been especially designed for adults and children older than or equal to 2 years of age. For children under the age of 2 years (and, in particular, those under the age of 6 months), the nervous system and, as such, the neurologic examination is continually in flux (e.g. what is normal in a 28-day-old is not necessarily normal in a 2-month-old child). The evaluation of encephalopathy and neurologic deficits in infants and young children will need to be done in an age-appropriate fashion, taking into account the age and level of development of the child.

d. Levels 2 or 3 of encephalitis are met if criteria (a + b + d) or (c + d) from the respective levels are fulfilled, and no exclusion criteria are met.

e. Note that only criteria 2 and 5 may be applicable in all age groups; other criteria for focal/mulitfocal neurologic signs may be age-dependent, and will not be applicable to all age groups.

f. Note that Level 2 of diagnostic certainty requires at least 2 of the listed criteria for inflammation, while Level 3 required only 1 criterion. This is in recognition that, in some cases of encephalitis, all listed criteria will either not be present, or such data will be unavailable. Thus, a clinical diagnosis of encephalitis should still be applicable, but will be of less diagnostic certainty than if sufficient criteria were present.

g. Electroencephalographic (EEG) findings consistent with encephalitis: EEG findings consistent with encephalitis include, but are not limited to: Diffuse or multifocal nonspecific (nonphysiologic) background slowing; periodic discharges or other encephalographic abnormalities may or may not be present.

h. Neuroimaging findings consistent with encephalitis: Neuroimaging findings consistent with encephalitis include, but are not limited to: head computed tomography (CT) displaying areas of hypodensity; contrast images demonstrating meningeal and parenchymal enhancement indicating meningeal and parenchymal inflammation, or gyral enhancement, brain/spine magnetic resonance imaging (MRI) displaying diffuse or multifocal areas of hyperintense signal on T2-weighted, diffusion-weighted image, or fluid-attenuation inversion recovery (FLAIR) sequences, suggestive of inflammation or demyelination.

i In certain situations, insufficient information will be available to make a definitive distinction between acute encephalitis and ADEM; in such instances, the Level of diagnostic certainty 3A should be used, and all attempts should be made to obtain additional information that will allow for further categorization of the case.

j. For example, neoplasm, toxic/metabolic encephalopathy, vascular disorder, trauma, etc.

k. Levels 2 or 3 of myelitis are met if criteria (a + b) from the respective levels are fulfilled, and no exclusion criteria are met.

l. Note that Level 2 of diagnostic certainty requires at least 2 of the listed criteria for inflammation, while Level 3 required only 1 criterion. This is in recognition that, in some cases of myelitis, all listed criteria will either not be present, or such data will be unavailable. Thus, a clinical diagnosis of encephalitis should still be applicable, but will be of less diagnostic certainty than if sufficient criteria were present.

m. Level 1 of ADEM is met if criterion (a) is met or if criteria (b + c + d) are fulfilled, and no exclusion criteria are met.

n. Absence of recurrence will be fulfilled only through long-term follow-up assessment. Lack of recurrence of neurologic symptoms within a 3-month period of first episode would be considered suggestive of a monophasic illness. A certain percentage of cases, however, will likely later be classified as multiple sclerosis. Diagnostic certainty is increased in direct correlation with duration of follow-up with absence of recurrence of illness.

o. Symptomatic nadir is defined at the point at which clinical symptoms are felt to be at the clinical worst; this nadir will need to be defined and identified by the health practitioner on a case-by-case basis; interval between illness onset and symptomatic nadir should be documented.

p. The absence of recurrence and monophasic nature of ADEM is useful as a distinguishing feature to discern ADEM from multiple sclerosis. It is recognized, however, that some authorities recognize an entity of "relapsing ADEM", which may represent a separate pathophysiologic entity from MS. However, the Working Group decided that recurrence of illness following a 3-month interval would be more likely representative of MS, and for the operational purposes of this definition, such recurrence would be operationally considered MS, and thus "not a case" of ADEM. Additionally, the development of acute demyelinating illness in a person with a known history of MS may be difficult to classify as either ADEM or an exacerbation of MS; however, most authorities would likely classify such an event as an MS exacerbation, with the understanding that such differentiation may be imperfect and uncertain.

q. Level 2 of ADEM is met if criteria (a + b + c) are fulfilled and no exclusion criteria are met.

Appendix: Features that may aid in distinguishing Acute Disseminated Encephalomyelitis (ADEM) from Multiple Sclerosis – per suggestions by the Brighton Collaboration Encephalitis Working Group

	ADEM	Multiple Sclerosis
Prodromal febrile illness	Common	Unusual
Signs and symptoms	Frequent widespread CNS disturbance; coma/drowsiness common	Frequently monosymptomatic
Temporal pattern of illness	Monophasic	Relapsing and remitting
Neuroimaging features	• High lesion load • Large, bilateral white matter lesions • Thalamic involvement sometimes present; • Lesions of same age	• Lower lesion load (generally) • Smaller plaques in deep white matter • Thalamic or other deep grey involvement unusual • Lesions of different ages
Cerebrospinal fluid	Oligoclonal bands frequently absent	Oligoclonal bands frequently present

4.1.6 Fatigue (8)

Level 1 of diagnostic certainty (persons ≥ 5 years of age)[a,b]

Level 1a (fatigue state)

- A new symptom[c,d] of fatigue (or a synonym),[e] *THAT IS*
- The primary complaint,[f] *AND IS*
- Not relieved by rest,[g] *AND*
- Interferes with an individual's function.[h]

Level 1b (specified fatigue syndrome)

- A new symptom[c] of fatigue (or a synonym),[e] *THAT IS*
- The primary complaint,[f] *AND IS*
- Not relieved by rest,[g] *AND*
- Interferes with an individual's function,[h] *AND WHICH IS*
- Accompanied by any of the following specified new symptoms[c] including post-exertion malaise,[i] impaired memory or concentration, unrefreshing sleep, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, or new headaches.[j]

Level 1c (other fatigue syndrome)

- A new symptom[c,d] of fatigue (or a synonym),[e] *THAT IS*
- The primary complaint,[f] *AND IS*
- Not relieved by rest,[g] *AND*
- Interferes with an individual's function,[h] *AND WHICH IS*
- Accompanied by other new symptoms[c] not specified in Level 1b.[k]

Further criteria required to achieve Levels 1a, b, and c

- The fatigue has been confirmed by a valid and reliable self-report measure[d] (see Appendix I), *AND*
- The functional impairment has been confirmed by a valid and reliable measure (see Appendix II).

Exclusion criteria required to achieve Levels 1a, b, and c

- *Concurrent onset of* medical or psychiatric disorders of which fatigue is a recognized symptom (see Appendix III), which have

been identified by appropriate laboratory tests (see Appendix IV) and a standardized psychiatric interview (see Appendix V) *AND*

- *Concomitant use* of a medicine or recreational drug recognized to cause fatigue (see Appendix VI).

Level 2 of diagnostic certainty (all age groups)[a,b]

Level 2a (fatigue state)

- A new symptom[c,d] of fatigue (or a synonym).[e]

Level 2b (specified fatigue syndrome)

- A new symptom[c,d] of fatigue (or a synonym),[e] *WHICH IS*
- Accompanied by any of the following specified new symptoms[c] including post-exertion malaise,[i] impaired memory or concentration, unrefreshing sleep, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, or new headaches.[j]

Level 2c (other fatigue syndrome)

- A new symptom[c,d] of fatigue (or a synonym),[e] *WHICH IS*
- Accompanied by other new symptomsc not specified in Level 2b.[k]

Exclusion criteria required to achieve Levels 2a, b and c

- *Known concurrent onset of* known medical or psychiatric disorders of which fatigue is a recognized symptom (see Appendix III), *AND*
- *Known concomitant use* of a medicine or recreational drug recognized to cause fatigue (see Appendix VI).

Level 3 of diagnostic certainty (all age groups)[a,b]

Level 3a (fatigue state)

- A new symptom[c,d] of fatigue (or a synonym).[e]

Level 3b (specified fatigue syndrome)

- A new symptom[c,d] of fatigue (or a synonym),[e] *WHICH IS*
- Accompanied by any of the following specified new symptoms[c] including post-exertion malaise,[i] impaired memory or concentration, unrefreshing sleep, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, or new headaches.[j]

Level 3c (other fatigue syndrome)

- A new symptom[c,d] of fatigue (or a synonym),[e] *WHICH IS*
- Accompanied by other new symptoms[c] not specified in Level 3b.[k]

Exclusion criteria required to achieve Levels 3a, b and c

- Any information about a concurrent medical or psychiatric disorder of which fatigue is a recognized symptom (see Appendix III), *AND/OR*
- Any information about concomitant use of a medicine or recreational drug known to cause fatigue (see Appendix VI).

Notes for fatigue case definition

Note: Refer to the full document for the guidelines and appendices mentioned in the case definition and in the notes below.

a. The Working Group considered that recognition of an unexplained fatigue state in children <5 years of age was problematic, hence only Levels 2 and 3 of the case definition can be reached in that age group.
b. Review of all criteria (inclusion AND exclusion) prior to categorization of a case is necessary.
c. Symptom is defined as "a phenomenon experienced by an individual as a departure from normal function, sensation, or appearance, generally indicating disease or disorder" (*9*). A "new" symptom implies a change from normal, or if the symptom was a pre-existing condition, then a change in character or severity is implied.
d. Investigators must describe the method(s) of collection. Symptoms can be collected as a spontaneous narrative, through clarifying questions, or actively solicited. The methods of data collection may differ depending on the research setting. The frequency of the symptoms reported likely varies significantly depending on the method of data collection used. In all children (<18 years of age), the parent or caregiver should ideally report on fatigue or synonyms for fatigue based on observation of the child, in addition to the child's self-report which should also be collected in children 5–17 years of age.
e. Synonyms for fatigue may include verbs, adjectives or nouns such as worn out, pooped, run down, lassitude, tiredness, exhausted, loss or lack of energy, lethargy. Synonyms are also culture- and language-specific and can be adjusted accordingly.
f. Primary complaint is equivalent to the principal or main complaint.
g. Rest may result in partial relief of the fatigue state, but return to pre-morbid status is not achieved.
h. Interference with individual's function means a reduction in daily function at work, school, social, or personal activities.
i. Post-exertion malaise needs to be out of proportion to the degree of exertion and may last >24 h.
j. One of the outcomes of adherence to the definition as described in Level 1b is the identification of CFS as defined by Fukuda et al. (*10*). Specifically, unexplained fatigue of greater than 6 months duration that is not relieved by rest and interferes with work, school, personal, and/or social activities and is accompanied by four of the eight specified symptoms would be required to fulfill this definition.
k. If one or more specified symptoms as well as non-specific symptoms are identified, the case should be coded as Level b.

4.1.7 Fever (11)

Level 1 of diagnostic certainty

- Fever is defined as the endogenous elevation of at least one measured body temperature of ≥38ºC.[a,b]

Level 2 of diagnostic certainty

- Not applicable.

Level 3 of diagnostic certainty

- Not applicable.

Notes for fever case definition

a. The value of ≥38ºC is accepted as reflecting an abnormal elevation of temperature, irrespective of device, anatomic site, age, or environmental conditions.

b. While it is recognized that this value is to some extent arbitrary, it is based upon a conservative interpretation of definitions proposed and used by clinicians, investigators, and the public at large.

4.1.8 Generalized convulsive seizure (7)

Level 1 of diagnostic certainty

- witnessed sudden loss of consciousness *AND*
- generalized,[a] tonic,[b] clonic,[c] tonic–clonic,[d] or atonic[e,f] motor manifestations.

Level 2 of diagnostic certainty

- history of unconsciousness *AND*
- generalized,[a] tonic,[b] clonic,[c] tonic–clonic,[d] or atonic[e,f] motor manifestations.

Level 3 of diagnostic certainty

- history of unconsciousness *AND*
- other generalized motor manifestations.

Notes for seizure case definition

a. Synonymous with: bilateral, more than minimal muscle involvement.
b. A sustained increase in muscle contraction lasting a few seconds to minutes.
c. Sudden, brief (<100 ms) involuntary contractions of the same muscle groups, regularly repetitive at a frequency of about two to three contractions/s.
d. A sequence consisting of a tonic followed by a clonic phase.
e. A sudden loss of tone in postural muscles, often preceded by a myoclonic jerk and precipitated by hyperventilation.
f. In the absence of: hypotonic hyporesponsive episode (as defined by the Brighton Collaboration), syncope, and myoclonic jerks.

4.1.9 Guillain–Barré syndrome and Fisher syndrome (12)

A. Guillain–Barré syndrome (GBS)[a,b,c]

Level 1 of diagnostic certainty

- Bilateral AND flaccid weakness of the limbs[d,e,f]

AND

- Decreased or absent deep tendon reflexes in weak limbs[g]

AND

- Monophasic illness pattern[h] AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[i]

AND

- Electrophysiologic findings consistent with GBS[j]

AND

- Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/μl)[k]

AND

- Absence of an identified alternative diagnosis for weakness (see Appendix A.3).[a]

Level 2 of diagnostic certainty

- Bilateral AND flaccid weakness of the limbs[d,e,f]

AND

- Decreased or absent deep tendon reflexes in weak limbs[g]

AND

- Monophasic illness pattern[h] AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[i]

AND

- CSF total white cell count <50 cells/µl (with or without CSF protein elevation above laboratory normal value)[k]

OR

- IF CSF not collected or results not available, electrophysiologic studies consistent with GBS[j]

AND

- Absence of identified alternative diagnosis for weakness (see Appendix A.3).[a]

Level 3 of diagnostic certainty

- Bilateral AND flaccid weakness of the limbs[d,e,f]

AND

- Decreased or absent deep tendon reflexes in weak limbs[g]

AND

- Monophasic illness pattern[h] AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[i]

AND

- Absence of identified alternative diagnosis for weakness (see Appendix A.3).[a]

B. Fisher syndrome (FS)[l]

Level 1 of diagnostic certainty

- Bilateral ophthalmoparesis AND bilateral reduced or absent tendon reflexes, AND ataxia[m]

AND

- Absence of limb weakness[n]

AND

- Monophasic illness pattern AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[o,p]

AND

- Cytoalbuminologic dissociation (i.e., elevation of cerebrospinal protein above the laboratory normal AND total CSF white cell count <50 cells/μl])[q]

AND

- Nerve conduction studies are normal, OR indicate involvement of sensory nerves only[r]

AND

- No alterations in consciousness or corticospinal tract signs[s]

AND

- Absence of identified alternative diagnosis.[t]

Level 2 of diagnostic certainty

- Bilateral ophthalmoparesis AND bilateral reduced or absent tendon reflexes AND ataxia[m]

AND

- Absence of limb weakness[n]

AND

- Monophasic illness pattern AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[o,p]

AND

- Cerebrospinal fluid (CSF) with a total white cell count <50 cells/μl])[q] (with or without CSF protein elevation above laboratory normal value)

OR

- Nerve conduction studies are normal, OR indicate involvement of sensory nerves only[r]

AND

- No alterations in consciousness or corticospinal tract signs[s]

AND

- Absence of identified alternative diagnosis.[t]

Level 3 of diagnostic certainty

- Bilateral ophthalmoparesis AND bilateral reduced or absent tendon reflexes AND ataxia[m]

AND

- Absence of limb weakness[n]

AND

- Monophasic illness pattern AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[o,p]

AND

- No alterations in consciousness or corticospinal tract signs[s]

AND

- Absence of identified alternative diagnosis.[t]

Notes for Guillain–Barré syndrome and Fisher syndrome case definitions

Note: Refer to the full document for the guidelines and appendices mentioned in notes below.

a. If an *alternative diagnosis* explaining flaccid weakness/paralysis is present (Appendix A.3), a diagnosis of Guillain–Barré syndrome is excluded. However, in many, if not most cases, a comprehensive documentation of testing for various other etiologies will either be incomplete or unavailable. These case definitions are provided to give guidance in the absence of detailed information on investigations for alternative etiologies of flaccid paralysis.

b. It is recognized that there are several clinical syndromes which are considered as part of the spectrum of Guillain–Barré syndrome that may not be captured under these case definitions. However, these are rare and comprise under 1% of overall GBS cases. Thus, the number of cases missed by these definitions is considered to be extremely low. An exception to this is the FS of ophthalmoplegia, ataxia, and loss of tendon reflexes which is generally considered to be a subtype of GBS (see FS case definition).

c. The clinical and electrophysiologic criteria specified in this document were designed to be applicable to all ages. The Working Group recognizes that neurologic features in infants and young children are continually developing and that assessment of infants can be difficult. However, GBS in children under 6 months of age is a very uncommon occurrence *(13)*. When possible, infants and children under 2 years of age should preferably be evaluated by a clinician familiar with the neurologic evaluation of young children, and such evaluations should be performed in an age-appropriate fashion, taking into account the changing neurologic features in the developing infant.

d. Weakness is usually, but not always, symmetric in nature, and usually has a pattern of progression from legs to arms (ascending). However, other patterns of progression may occur (e.g., beginning in the arms). The degree of weakness can range from mild to moderate to severe, i.e., complete paralysis.

e. Respiratory or cranial nerve-innervated muscles may also be involved.

f. It is important that strength be assessed in a manner that takes into account subject age, sex, and level of functioning.

g. Decreased or absent tendon reflexes may also be seen in limbs without weakness. However, to meet case definition criteria, decreased or absent tendon reflexes must be observed in weak limbs.

h. Fluctuations in level of weakness, before reaching nadir, or during the plateau or improvement phases, occur in some cases, usually associated with the use of disease-modifying therapies. Such fluctuations usually occur within the first 9 weeks after onset *(14)* and are followed by eventual improvement.

i. The eventual outcome is either stabilization at nadir OR subsequent improvement OR death.

j. Electrophysiologic patterns consistent with polyneuropathy of the types described for GBS *(15)*. Electrophysiologic studies performed sooner than 7 days after weakness onset may be normal and should thus be repeated at a later time if possible, and "normal" studies may occur in otherwise typical cases of GBS. However, cases with persistently "normal" studies will not meet Level 1 criteria.

k. CSF (cerebrospinal fluid) protein concentrations should be elevated above what is considered normal reference values for the testing laboratory. CSF may be "normal" in otherwise typical cases of GBS; this is particularly true within the first week of illness. However, cases with persistently "normal" CSF, or CSF with ≥50 WBC, will not meet Level 1 criteria.

l If an *alternative diagnosis* explaining the triad, including (but not limited to) botulism, diphtheria, and Wernicke's encephalopathy, is present (Appendix A.3), a diagnosis of FS is excluded. However, in many, if not most cases, a comprehensive documentation of testing for various other etiologies will either be incomplete or unavailable. These case definitions are provided to give guidance in the absence of detailed information on investigations for alternative etiologies of this clinical triad.

m. Ophthalmoparesis, tendon reflexes, and ataxia are relatively symmetric. Ptosis or pupillary abnormalities may be present in the setting of the ophthalmoplegia. The clinical severity of each component may vary from partial to complete. Hypo- or areflexia tends to be diffuse/global, and symmetric. However, selective involvement of upper or lower extremity reflexes may be seen. Facial and bulbar weakness may also be features.

n. Presence of limb weakness would suggest a diagnosis of Guillain-Barré syndrome (GBS) (see case definition for GBS).

o. Improvement of symptoms may occur with or without treatment.

p. The eventual outcome is either stabilization of symptoms at nadir OR subsequent improvement OR death.

q. CSF protein levels should be elevated above what is considered normal reference values for the testing laboratory. CSF may be "normal" in otherwise typical cases of FS; this is particularly true in the first week of illness. However, cases with persistently "normal" CSF will not meet Level 1 criteria.

r. Motor nerve conduction abnormalities in this clinical setting likely indicate GBS/FS overlap.

s. Presence of these findings, including extensor plantar responses, would be suggestive of Bickerstaff's Brainstem Encephalitis. Brain magnetic resonance imaging (MRI), if performed, should be normal, or, if abnormal, should not demonstrate brainstem lesions consistent with encephalitis. MRI findings that would be suggestive of Bickerstaff's Brainstem Encephalitis would include: presence of patchy or confluent lesions that are hypointense on T1-weighted images and hyperintense on T2- and fluid-attenuated inversion recovery (FLAIR) sequences in the brainstem (with or without involvement of other cerebral structures).

t. Including, but not limited to, Wernicke's encephalopathy, botulism, diphtheria.

4.1.10 Hypotonic-hyporesponsive episode (HHE) in early childhood (<2 years of age) (16)

Level 1 of diagnostic certainty

- The sudden onset of
- Hypotonia (muscle limpness) *AND*
- Hyporesponsiveness (reduced responsiveness) or unresponsiveness *AND*
- Pallor or cyanosis

Level 2 of diagnostic certainty

The sudden onset of

- Hyporesponsiveness (reduced responsiveness) or unresponsiveness *AND*
- Pallor or cyanosis *AND*
- Muscle tone unknown

OR

- Hypotonia (muscle limpness)[a] *AND*
- Hyporesponsiveness (reduced responsiveness) or unresponsiveness[a] *AND*
- Skin colour unknown

Level 3 of diagnostic certainty

The sudden onset of

- Hyporesponsiveness (reduced responsiveness) or unresponsiveness *AND*
- Pallor or cyanosis *AND*
- Normal muscle tone

OR

- Hypotonia (muscle limpness) *AND*
- Pallor or cyanosis *AND*
- Level of responsiveness unknown

Notes for HHE case definition

a. This combination of signs forming level 2 of diagnostic certainty is similar to level 2 of diagnostic certainty for atonic seizures as defined by the Brighton Collaboration (*7*). Of note, atonic seizures are generally very brief and the post-ictal state is not one of un- or hypo-responsiveness. It is left to the assessors' discretion whether the episode will be recorded as "HHE level 3" or "seizure level 2", depending on the overall presentation of the case.

4.1.11 Persistent crying[a] in infants and children (17)

Level 1 of diagnostic certainty

The *presence* of crying[b] which is

- continuous[c] *AND*
- unaltered for ≥3 h.

Level 2 of diagnostic certainty

The *presence* of crying which is

- continuous[c] *AND*
- likely to be unaltered for >3 h

OR

- unaltered for >3 h *AND*
- likely to be continuous.

Level 3 of diagnostic certainty

Not applicable

Notes for persistent crying case definition

a. Screaming is a louder form of crying.

b. Parents or other caregivers may describe the quality of the cry with such words as "fearful", "angry", "sorrowful", "in pain", "pitiful", "plaintiff", "never heard before in this child".

c. Not episodic, not interrupted within the time period of 3 h (e.g. by naps).

4.1.12 Rash including mucosal involvement (18)

Level 1 of diagnostic certainty

- A skin or mucosal change (either new or an exacerbation of a previous condition) following immunization,[a,b] *THAT*
- consists of a clearly identified primary lesion and/or secondary skin change, *AND*
- is documented with the standard terminology found in Appendix A, *AND*
- is documented by a health-care provider or other person trained in identifying mucocutaneous reactions.[c]

Level 2 of diagnostic certainty

- A skin or mucosal change (either new or an exacerbation of a previous condition) following immunization,[a,b] *FOR WHICH*

- a morphologic description has been provided (but Level 1 criteria are not met).

Level 3 of diagnostic certainty

- A skin or mucosal change (either new or an exacerbation of a previous condition) following immunization without morphologic description.[a,b]

Notes for rash case definition

Note: Refer to the full document for the guidelines and appendices mentioned in the case definition and in the notes below.

a. Because too little is known about precise time intervals of skin or mucosal changes following immunization, and time intervals for different lesions may differ markedly, there is no time interval specified between the vaccination and the development of the skin or mucosal change.

b. Several more specific syndromes have cutaneous manifestations that may meet the criteria for this case definition (e.g. cellulitis). If the criteria for a more specific case definition are met, the event should be classified to that case definition.

c. Health-care provider is not further defined, because of country-specific differences; qualifying professionals will have to be decided upon in the respective country. In this case definition, this phrase is meant to denote someone with sufficient training to distinguish a rash from other dermatologic findings such as ecchymosis, congenital pigmentation variations, etc. It was decided by the Working Group that the criterion "documented by a health-care provider" increased the diagnostic certainty for mucocutaneous changes following vaccination, and thus was included into Level 1 of this case definition.

4.1.13 Thrombocytopenia (TP) (19)

Level 1 of diagnostic certainty (confirmed TP)

- Platelet count[a] less than 150×10^9 L^{-1}

AND

- confirmed by blood smear examination OR the presence of clinical signs and symptoms of spontaneous bleeding.[b]

Level 2 of diagnostic certainty (unconfirmed TP)

- Platelet count[a] less than 150×10^9 L^{-1}.

Level 3 of diagnostic certainty

Not applicable.

Notes for thrombocytopenia case definition

a. Measured by an automated hematology analyzer or assessed by hand count of platelets on a cell count slide.

b. Presentations of spontaneous (i.e. non-traumatic) bleeding include purpura (i.e. petechiae, purpura *sensu stricto*, ecchymosis), hemorrhagic oozing of skin lesions including rashes, hematoma, bruising, hematemesis, hematochezia, occult bleeding per rectum, epistaxis, hemoptysis, hematuria, vaginal bleeding other than menstruation, conjunctival bleeding, intracranial bleeding.

4.1.14 Unexplained sudden death, including sudden infant death symdrome (SIDS), in the first and second years of life (20)

Level 1 of diagnostic certainty

(Unexplained after complete postmortem investigation)

- Sudden death of any child under 2 years of age which remains unexplained[a] *after excluding other causes of death*[b] by
  1. Review of clinical history[c] *AND*
  2. History of final events[c] *AND*
  3. Review of *complete autopsy* report with a standardize[d] protocold that includes
     - Macroscopic examination *AND*
     - Microscopic examination *AND*
     - Microbiologic samples *AND*
     - Toxicological samples *AND*
     - Screen for metabolic diseases *AND*
     - Radiological studies

AND

- Review of circumstances of death including examination of death scene performed by a suitably qualified person, such as homicide investigator or medical scene investigator or medical examiner.[c]

Level 2 of diagnostic certainty

(Unexplained after clinical and final event history and autopsy)

- Sudden death of any child under 2 years of age which remains unexplained[a] *after excluding other causes of death at least by*

1. Review of clinical history[c] *AND*
2. History of final events[c] *AND*
3. Review of incomplete[e] autopsy result.

Level 3 of diagnostic certainty

(Unexplained after clinical and final event history but without autopsy[f])

- Sudden death of any child under 2 years of age which remains unexplained[a] *after excluding other causes of death at least by*
  1. Review of clinical history *AND*
  2. History of final events.

For any level of diagnostic certainty

- Children under 2 years of age found unresponsive who are resuscitated and later die are included if they otherwise meet the criteria.

Notes for unexplained sudden death case definition

a. All deaths without an explained cause of death are included. Deaths labeled as "unascertained" or "possible" SIDS should be included if they otherwise meet the criteria. All "borderline cases" should be included.

b. The original or a copy of the full autopsy report should be reviewed for completeness of postmortem investigation for Level 1. Equivalent information may be obtained from the medical examiner or pathologist. Reports diagnosing SIDS and labeled as "complete autopsy" but without data on investigations performed are Level 2 cases. If necessary, autopsy and other reports may be "anonymized" by removal of personal identification to comply with data privacy regulations.

c. The use of the SUIDI (Sudden, Unexplained Infant Death Initiative) Reporting Form is recommended (*21*). Review of house, room, and cot or bed should be performed even if the death might have occurred in an emergency department.

d. The use of the International Autopsy Protocol is recommended (*22, 23*).

e. At least one investigation (i.e. macroscopic or microscopic examination, microbiologic, toxicological, metabolic, or radiological studies) is missing.

f. The use of the standard verbal autopsy method is recommended in settings where autopsies are not usually performed (*24*).

Case definitions for injection site reactions

4.1.15 Abscess at injection site[a] (25)

Abscess at injection site is a localized soft tissue[b] collection of material, occurring at the site of immunization and is defined by:

Level 1 of diagnostic certainty

A. Abscess of infectious etiology

- Spontaneous or surgical[c] drainage of material from the mass;

AND

- Laboratory confirmation (Gram stain, culture or other tests) of microbiological organisms with or without polymorphonuclear leukocytes in material drained or aspirated from mass.

Abscesses of infectious etiology may be accompanied by fever and/or regional lymphadenopathy.

B. Sterile abscess

- Spontaneous or surgical[c] drainage of material from the mass;

AND

- Material obtained from the mass prior to initiating antimicrobial therapy, but with negative evaluation for infectious etiology (which may include Gram stain, cultures or other tests).

Sterile abscesses are typically not accompanied by fever[d] and/or regional lymphadenopathy.

Level 2 of diagnostic certainty

In settings where laboratory evaluation for infectious etiology (Gram stain, cultures, or other technique) was either not performed, performed after starting antimicrobial therapy, or not reported.

A. Abscess of infectious etiology

- Spontaneous or surgicalc drainage of purulent[e] material from the mass;

OR

- Collection of material diagnosed by an imaging technique (e.g. sonogram, CT, MRI, or other modality) or fluctuance:[f] *AND*

- Localized sign(s) of inflammation including at least one of the following: erythema, pain to light touch, or warm to touch at the injection site;

AND

- Resolution /improvement temporally related to antimicrobial therapy.

Abscesses of infectious etiology may be accompanied by fever[d] and/or regional lymphadenopathy.

B. Sterile abscess

- Spontaneous or surgical[c] drainage of non-purulent[e] material from the mass; *OR*
- Collection of material e.g. fluid diagnosed by imaging technique (e.g. sonogram, CT, MRI, or other modality) or fluctuance;[f]

AND

- The absence of signs of local inflammation such as erythema, pain to light touch, and warm to touch at the injection site; *OR*
- No resolution/improvement temporally related to antimicrobial therapy.

Sterile abscesses are typically not accompanied by fever[d] and/or regional lymphadenopathy.

C. Type indeterminant

Insufficient information to determine whether abscess is of infectious etiology or a sterile abscess; i.e. report of incision and drainage of the injection site mass but no culture results reported, or report of the collection of material at the injection site demonstrated by an imaging technique but clinical symptoms or response to antimicrobial therapy not reported.

Level 3 of diagnostic certainty

Not applicable.

For all levels listed above, the following in and of themselves do not constitute abscesses at the injection site:

- superficial vesicles or pustules on the skin,
- suppurative lymph nodes adjacent to the site of immunization,
- septic joints adjacent to the site of immunization, or

- cellulitis and nodule at injection site (see the respective Brighton Collaboration documents at: https://brightoncollaboration.org/public).

Notes for abscess case definition

a. Review of all criteria (inclusion AND exclusion) prior to categorization of a case is necessary.
b. In subcutaneous tissue, fat, fascia or muscle.
c. Surgical drainage may consist of needle aspiration, and/or complete or partial incision.
d. Fever is defined as the endogenous elevation of at least one measured body temperature of ≥38°C (*11*).
e. Purulent is defined as containing or consisting of pus, which may be cloudy in appearance and/or foul-smelling.
f. Fluctuance is defined as wavelike motion on palpation due to liquid content.

4.1.16 Cellulitis at injection site (26)

Cellulitis is defined[a] as an acute, infectious,[b] and expanding inflammatory condition of the skin that is characterized by the following inclusion and exclusion criteria. Of note, cellulitis may be accompanied by fever[c] and/or regional lymphadenopathy, however, their presence or absence does not influence the level of diagnostic certainty.

Level 1a of diagnostic certainty

At least three of the following four signs/symptoms:

- Localized pain or tenderness[d] (pain to touch);
- Erythema;[d]
- Induration[d] or swelling[e];
- Warmth;[d]

AND

- Reaction is at the injection site[f]; *AND*
- Laboratory-confirmation by culture.[g]

If known,[h] exclusion criteria are:

- Spontaneous rapid resolution;[i] *AND/OR*
- Fluctuance.[j]

OR

Level 1b of diagnostic certainty

- A diagnosis of cellulitis by a qualified health-care provider[k]; *THAT IS*
- At the injection site[f]; *AND*
- Laboratory-confirmation by culture.[g]

If known,[h] exclusion criteria are:

- Spontaneous rapid resolution;[i] *AND/OR*
- Fluctuance.[j]

Level 2 of diagnostic certainty

At least three of the following four signs/symptoms:

- Localized pain or tenderness[d] (pain to touch);
- Erythema;[d]
- Induration[d] or swelling[e];
- Warmth;[d]

AND

- Reaction is at the injection site[f]; *AND*
- Has been diagnosed by a qualified health-care provider.[g]

If known,[h] exclusion criteria are:

- Spontaneous rapid resolution[i]; *AND/OR*
- Fluctuance.[j]

Level 3 of diagnostic certainty

- At least three of the following four signs/symptoms:
- Localized pain or tenderness[d] (pain to touch);
- Erythema;[d]
- Induration[d] or swelling[e];
- Warmth;[d]

AND

- Reaction is at the injection site[f]; *AND*

- Has been reported by any person (not specified as a qualified health-care provider[g]).

If known,[h] exclusion criteria are:

- Spontaneous rapid resolution[i]; *AND/OR*
- Fluctuance.[j]

Notes for cellulitis case definition

a. All criteria (inclusion and exclusion) apply to the time of diagnosis, and review of all criteria (inclusion and exclusion) prior to categorization of a case is necessary. Follow-up information can be considered if sufficiently documented and reported in a timely manner.

b. The infectious agent is not to solely include the vaccine antigen itself.

c. Fever is defined as ≥38ºC (*11*).

d. Cellulitis at injection site is distinguished from post-injection erythema, tenderness, and induration by the more intense erythema, tenderness to light touch, at least moderate induration, and substantial local warmth.

e. See respective Brighton Collaboration case definitions for swelling and induration at injection site. Cellulitis is typically accompanied by induration and not swelling. However, for reporting and coding purposes, either is acceptable.

f. In subcutaneous tissue, fat, fascia, or muscle.

g. The diagnosis of cellulitis may be clinical or laboratory confirmed. An aspirate from the involved area should be done for a laboratory culture confirmation of the etiological agent. It is less common but more definitive in confirming cellulitis of infectious etiology. Similarly, a positive recovery of a recognized pathogen such as *S. aureus* or Group A beta hemolytic *Streptococcus* from a blood culture in the presence of at least 3 listed signs/symptoms would confirm the presence of cellulitis. Laboratory confirmation facilitates the differentiation of cellulitis from post-immunization erythema or induration. In the absence of laboratory confirmation, diagnosis of cellulitis by a qualified health-care provider or treatment with antimicrobial agents may increase the likelihood of the correctness of the diagnosis. Health-care provider is not further defined, because of country-specific differences; qualifying professionals will have to be decided upon in the respective country.

h. Lack of information on exclusion criteria does not preclude the diagnosis of cellulitis; however, if exclusion criteria are present, the event needs to be rejected as cellulitis at injection site.

i. Cellulitis at injection site is associated with a prolonged duration; erythema and induration at injection site are usually spontaneously resolving within 2 days, whereas cellulitis does usually not resolve spontaneously.

j. See Brighton Collaboration case definition for abscess at injection site (https://brightoncollaboration.org/public): if the involved area develops fluctuance, or ultrasound evidence of abscess, then the event should be reported as an abscess.

k. A qualified health-care provider diagnosis alone with laboratory confirmation is acceptable as Level 1 evidence, because health-care providers typically report a diagnosis rather than individual symptoms.

4.1.17 Induration at or near injection site (27)

Level 1 of diagnostic certainty

- Palpable thickening, firmness, or hardening of soft tissue,[a]

AND

- is assessed and reported by a health-care provider.[b]

Level 2 of diagnostic certainty

- Palpable thickening, firmness, or hardening of soft tissue,[a]

AND

- is assessed and reported by any person (not specified as a health-care provider).

Level 3 of diagnostic certainty

Not applicable.

For all levels

Induration should be described as follows for each level of diagnostic certainty:

(a) induration clearly includes the injection site(s) (approximate point of needle entry),

OR

(b) local induration not clearly including the injection site(s).

Induration needs to be carefully distinguished from abscess, nodule, cellulitis and swelling. It is recognized that distinguishing them clinically can sometimes be difficult. Moreover, induration can exist independently, concomitantly to, or as part of the other event. Particular focus should be given to differentiate swelling from induration. Swelling is typically caused by fluid infiltration in tissue, and although swelling may be either soft (typically) or firm (less typical) depending on the space available for fluid to disperse, it can best be described by looking and measuring. Induration is usually well demarcated with palpable borders, can be visible (raised or sunken compared to surrounding skin), is often 'woody' to touch and has a flat shape (versus the rounder shape of a nodule); it can best be described by palpation. The appropriate Brighton Collaboration documents

(see at: https://brightoncollaboration.org/public) defining these conditions could be consulted and the local reaction(s), which best fits the description should be considered.

Notes for induration case definition

a. In subcutaneous tissue, fat, fascia, or muscle.

b. Health-care provider is not further defined, because of country-specific differences; qualifying professionals will have to be decided upon in the respective country.

4.1.18 Local reaction[a] at or near injection site (28)

Level 1 of diagnostic certainty

Any description of morphological or physiological[b] change at or near the injection site[c,d]

THAT IS

- Described or identified by a health-care provider.[e]

Level 2 of diagnostic certainty

- Any description of morphological or physiological change at or near the injection site

THAT IS

- Described or identified by any other person.[f]

Level 3 of diagnostic certainty

Not applicable.

Exclusion Criteria

A systemic reaction which includes the injection site, e.g. generalized urticaria, *OR*

Other distinct entities or conditions like lymphadenopathy that may be near the injection site.

Notes for local reaction case definition

Note: Refer to the full document for the guidelines and appendices mentioned in notes below.

a. In addition to the levels of diagnostic certainty, events that do not meet the case definition are sometimes reported as local reactions. Such events can be described in the analysis as reported events with insufficient evidence to meet the definition (e.g. if the location of the event in relation to the injection site is unknown). Events that meet an exclusion criterion or are known to lack a necessary criterion should be listed as reported events that have been determined not to be a case (see guideline 32).

b. A morphological or physiological change at or near the injection site refers to local reactions such as swelling, erythema, pain, warmth as listed by the Working Group in Appendix A.

c. At or near the injection site includes the injection site, is adjacent to the injection site, or is a reaction which may shift slightly away from the injection site due to gravity, as may occur, e.g. with swelling or hematoma.

d. Reference the algorithm (Appendix B) and/or guidelines Section 3.1.5 for a more comprehensive assessment of the adverse event.

e. Health-care provider is not further defined, because of country-specific differences; qualifying professionals will have to be decided upon in the respective country. In this case definition, this phrase is meant to denote someone with sufficient training to assess a local reaction following immunization.

f. Reported by any person not specified as a health-care provider.

4.1.19 Nodule at injection site (29)

A nodule[a] at injection site is defined[b] by

Level 1 of diagnostic certainty

- The presence of a discrete or well-demarcated soft tissue mass or lump

THAT IS

- firm *AND*
- is at the injection site[c].

There may be additional less discrete, softer swelling surrounding the nodule at the injection site, especially early in its development. There may also be tenderness and pruritus.

In the *absence* of

- abscess formation[d] *AND*
- erythema *AND*
- warmth.

Level 2 of diagnostic certainty

Not applicable.

Level 3 of diagnostic certainty

Not applicable.

Notes for nodule case definition

a. Sometimes referred to as a subcutaneous nodule, antigen cyst, or granuloma.
b. All criteria apply to the time of diagnosis
c. In subcutaneous tissue, fat, fascia, or muscle.
d. See Brighton Collaboration case definition for abscess at injection site: localized soft tissue collection of fluid determined clinically, by spontaneous or surgical drainage, or by an imaging technique.

4.1.20 Swelling at or near injection site (30)

Level 1 of diagnostic certainty[a]

- Visible enlargement of an injected limb with or without objective measurement;

AND

- Assessed by a health-care provider.[b]

Level 2 of diagnostic certainty[a]

- Visible enlargement of an injected limb with or without objective measurement;

AND

- Assessed by any person (not specified as a health-care provider).[b]

Level 3 of diagnostic certainty

Not applicable.

For all levels

Extension of swelling should be described as follows for each level of diagnostic certainty:

(a) Swelling clearly including injection site(s) (approximate point of needle entry).

(b) Local swelling, near to, but not clearly including the injection site(s).

(c) "Joint-to-joint" or "crossing-joint". "Joint-to-joint" means that the swelling includes the entire portion of the limb between joints, e.g. upper limb (i.e. from shoulder to elbow), and "crossing joints" means that the swelling crosses at least one joint (e.g. the elbow joint).

The swelling may be accompanied by erythema and tenderness. Swelling needs to be carefully distinguished from abscess, nodule, cellulitis and induration. It is recognized that distinguishing them clinically can sometimes be difficult. Moreover, swelling can exist independently, concomitantly to or as part of the other event. Particular focus should be given to differentiate swelling from induration. Swelling is typically caused by fluid infiltration in tissue, and although swelling may be either soft (typically) or firm (less typical) depending on the space available for fluid to disperse; it can best be described by looking and measuring. Induration usually has well-demarcated palpable borders, can be visible (raised or sunken compared to surrounding skin), is often 'woody' to touch and has a flat shape (versus the rounder shape of a nodule); it can best be described by palpation. The appropriate Brighton Collaboration documents (see at: https://brightoncollaboration.org/public) defining these conditions could be consulted and the local reaction(s), which best fits the description should be considered.

Notes for swelling case definition

Note: Refer to the full document for the guidelines and appendices mentioned in notes below.

a. Where possible, the swelling should be measured using valid instruments. It is considered that a valid measurement could be difficult to obtain outside the context of the controlled conditions of a clinical trial or prospective epidemiological study with a pre-defined protocol. Standardized and pre-tested tools and methods could be used, such as a caliper or pre-and post-injection measurement of the limb circumference at the injection site and/or at mid-limb. Caution should be used in the interpretation of tape measurements of the ipsi- and contra-lateral limbs given natural differences due to single handedness (refer to guidelines 21 and 33).

b. Health-care provider is not further defined, because of country-specific differences; qualifying providers will have to be decided upon in the respective country.

Case definitions for vaccinia-related adverse events

4.1.21 Eczema vaccinatum (EV) following exposure to vaccinia virus (31)

For all levels of diagnostic certainty

Symptoms or signs of a systemic viral illness, such as fever (≥100.4 °F [≥38°C][a]), malaise, or prostration, as well as lymphadenopathy, which is often generalized, usually occurs and may be present as early as 2 days after contact/exposure. Bacterial infections of the skin may coexist or mimic EV.

Level 1 of diagnostic certainty

- History or present evidence of atopic dermatitis[b] (eczema, atopic eczema) or Darier's disease or presence of skin conditions with loss of epithelial integrity;

AND

- Papules, vesicles or pustules;[c] which are
- Concentrated in localized areas[d] or in severe cases may involve the entire body;

AND

- Laboratory confirmation (positive vaccinia-virus-specific PCR or culture)[e] of vaccinia infection from the blood or lesions other than the vaccination site.

Level 2 of diagnostic certainty

- A person recently vaccinated or known to be a close contact of a recent vaccinee[f];

AND

- History or present evidence of atopic dermatitis[b] (eczema, atopic eczema) or Darier's disease or presence of skin conditions with loss of epithelial integrity;

AND

- Presence of lesions between days 4 and 28 after exposure to vaccinia virus:
- Papules, vesicles, or pustules;[c] which are
- Concentrated in localized areas[d] or in severe cases may involve the entire body;

AND

- Laboratory evaluation for orthopox viruses[g] other than vaccinia virus, and for other causes of papular or vesicular eruptions[h] was performed and found to be negative.

Level 3 of diagnostic certainty

- A person recently vaccinated or known to be a close contact of a recent vaccinee;[f]

AND

- History or present evidence of atopic dermatitis[b] (eczema, atopic eczema) or Darier's disease or presence of skin conditions with loss of epithelial integrity;

AND

- Lesions occur between 0 and 28[i] days after exposure to vaccinia virus; and are
- Papules, vesicles, or pustules;[c] which are
- Concentrated in localized areas[d] or in severe cases may involve the entire body;

AND

- Absence of laboratory investigation for vaccinia virus or other etiologies.

Notes for eczema vaccinatum case definition

Note: Refer to the full document for the guidelines and appendices mentioned in notes below.

a. See the Brighton Collaboration's definition for fever as adverse event following immunization. Available at https://brightoncollaboration.org/public.

b. It is recommended to consult current definitions for atopic dermatitis. Because of ongoing diversity in opinions by experts, the Brighton Collaboration Vaccinia Virus Vaccine Adverse Events working group refrains from recommending any one definition.

c. In a vaccinee, lesions often are temporally newer/less mature than the lesion at the vaccination site. Coalescence of at least some lesions within 5 days of their appearance is typical and some large (>5 cm in diameter), confluent areas of affected skin occur. During the papule phase, 50 or more lesions in defined areas can occur.

d. Lesions are most dense on anterior elbow creases, popliteal fossae, or central face (i.e. in area defined by lines drawn from lateral edges of eyebrows to chin, across bottom of chin, and across top of eyebrows) – or – in patients with a known history of atopic dermatitis or Darier's disease, lesions are most dense where dermatitis is/has been most active.

e. For more detailed information on laboratory testing for vaccinia virus, see Appendix A.
f. Examples of close contact would include direct (touching, sexual activity, or close contact sports activities, etc.) or (rarely) indirect (via shared bedding, clothing, wash cloths, inadequately sterilized medical devices, etc.) contact.
g. Laboratory testing for monkeypox or cowpox or variola is only indicated if recently in endemic area or history of contact with infected animals or persons.
h. Other papulo-vesicular conditions include: herpes simplex, varicella, rickettsialpox, scabies, drug eruptions, and allergic/contact dermatitis, mycoplasma pneumonia; see a list of infectious and non-infectious conditions in: 2nd Edition of Long, Pickering, Prober: Principles and Practice of Pediatric Infectious Diseases, p. 436. Laboratory evidence of herpes simplex virus or varicella-zoster virus includes viral culture (shell viral assay), direct fluorescent antibody tests, and Tzanck smears. Viral cultures, direct fluorescent antibody tests, and Tzanck smears are most reliable if performed on a vesicle/bulla.
i. Although it is extremely unlikely that EV will occur <4 days post exposure to vaccinia virus, the broader time window is designed to capture potential cases where other aspects of the definition are met, but the vaccination and onset dates may be askew.

4.1.22 Generalized vaccinia (GV) following exposure to vaccinia virus[a] (32)

Level 1 of diagnostic certainty[b]

- Lesions that are vesicles and/or pustules,[c] *AND*
- The lesions occur at four or more distinct areas of the body, and at sites removed from the initial vaccination site,[d,e] *AND*
- Laboratory confirmation (positive vaccinia-virus-specific PCR or culture)[f] of vaccinia infection from the blood or lesions other than the vaccination site.

Level 2 of diagnostic certainty[b]

- A person recently vaccinated or known to be a close contact of a recent vaccinee,[g]

AND

- Lesions that are papules, vesicles, and/or pustules,[c] *AND*
- The lesions occur at four or more distinct areas of the body, and at sites removed from the initial vaccination site,[d,e] *AND*
- The lesions have their onset between day 4 and 28 after exposure,

AND

- Laboratory evaluation for orthopox viruses[h] other than vaccinia, and for other causes of papular or vesicular eruptions[i] was performed and found to be negative.

Level 3 of diagnostic certainty[b]

- A person recently vaccinated or known to be a close contact of a recent vaccinee,[g]

AND

- Lesions are papules, vesicles, and/or pustules,[c] *AND*
- The lesions occur at any number of distinct areas at sites removed from the initial vaccination site,[d] *AND*
- The lesions occur between day 0 and 28[j] after exposure,

AND

- Clinical presentation that is not clearly consistent with other known causes of vesicular-pustular disease (e.g. chickenpox),

AND

- If laboratory evidence is available, then laboratory evaluation for orthopox viruses[h] other than vaccinia, and for other causes of papular or vesicular eruptions[i] has to be found to be negative.

Exclusion criterion required for all levels of diagnostic certainty

- A clinical history and distribution consistent with lesions of inadvertent inoculation.[k]

Notes for generalized vaccinia case definition

Note: Refer to the full document for the guidelines and appendices mentioned in notes below.

a. Attention: With a history of eczema, atopic dermatitis or Darier's disease (keratosis follicularis), refer to the Brighton Collaboration case definition of Eczema Vaccinatum (EV). If the criteria of Levels 1, 2, or 3 of diagnostic certainty of EV are not met, return to this case definition.

b. Review of all criteria (inclusion and exclusion) prior to categorization of a case is necessary. All criteria (inclusion and exclusion) apply to the time of diagnosis.

c. GV lesions progress through similar stages as the vaccination site, though often at an accelerated pace and sometimes with an attenuated response. GV lesions begin as papules and progress to vesicles then pustules.

d. GV has generally been described as between 4 and 50 lesions. Because GV may occur with less than four lesions, distinguishing GV from inadvertent inoculation in these cases may be difficult.

e. For the purpose of this definition, areas of involvement can be classified into the following groups: head, chest, back, abdomen, pelvic area including buttocks, upper arm (right [R.] or left [L.]), forearm including hand (R. or L.), thigh (R. or L.), leg including foot (R. or L.).

f. For more detailed information on laboratory testing for vaccinia virus, see Appendix A.

g. Examples of close contact would include direct (touching, sexual activity, or close contact sports activities) or (rarely) indirect (via shared bedding, clothing, wash cloths, inadequately sterilized medical devices, etc.) contact.

h. Laboratory testing for monkeypox or cowpox or variola is only indicated if recently in an endemic area or if there is a history of contact with infected animals or persons.

i. Other papulo-vesicular conditions include: herpes simplex, varicella, rickettsialpox, scabies, drug eruptions, allergic/contact dermatitis, and mycoplasma pneumonia; see a list of infectious and non-infectious conditions in: 2nd edition of Long, Pickering, Prober: Principles and Practice of Pediatric Infectious Diseases, p. 436. Laboratory evidence of herpes simplex virus or varicella-zoster virus includes viral culture (shell viral assay), direct fluorescent antibody tests, and Tzanck smears. Viral cultures, direct fluorescent antibody tests, and Tzanck smears are most reliable if performed on a vesicle/bulla.

j. Although it is extremely unlikely that GV will occur <4 days post exposure to vaccinia virus, the broader time window is designed to capture potential cases where other aspects of the definition are met, but the vaccination and onset dates may be askew.

k. Common sites for inadvertent inoculation are the face, eyelids, nose, mouth, genitalia, and anus. Uncommon sites for inadvertent inoculation include the back and legs. Often inadvertent inoculation is associated with a history of scratching preceding the development of the lesions. For more details, see the Brighton Collaboration's case definition of inadvertent inoculation.

4.1.23 Inadvertent inoculation[a] following exposure to vaccinia virus (33)

Level 1 of diagnostic certainty[b]

- The presence of a localized[c] cutaneous or mucosal lesion, or corneal ulceration(s),

AND

In a vaccinee:

- the lesion is at an anatomical site(s) other than the vaccination site, *OR*

If the patient has not received smallpox vaccination:

- the lesion is at any localizedc cutaneous, mucosal or corneal site(s),

AND

- there is laboratory confirmation (positive vaccinia virus-specific polymerase chain reaction or culture)[d] of vaccinia virus infection from the blood or lesions other than the vaccination site.

Level 2 of diagnostic certainty[b]

- The presence of one or more skin lesion(s) with either witnessed, or history of, localized[c] progressive lesion(s) (i.e. papule, vesicle, pustule, and/or scab[e]), *AND/OR*
- The presence of one or more mucosal lesion(s)f with either witnessed, or history of, progression of lesion(s) through at least two different stages (i.e. papule, vesicle, and/or pustule), which are unlikely to form a scab[e], *AND/OR*
- Conjunctival vesicular lesion(s) which ulcerate[g] over a period of <5 days, *AND/OR*
- Corneal lesion(s) that, in the opinion of an expert[h], are consistent with vaccinia keratitis[i],

AND

In a vaccinee:

- The lesion is at an anatomical site(s) other than the vaccination site, *AND*
- Onset of the papule(s) is 4–28 days post vaccination, *OR*

If the patient has not received smallpox vaccine:

- Onset of the papule(s) is 4–28 days post exposure to vaccinia virus.

Level 3 of diagnostic certainty[b]

- Localized[c] lesion(s) (skin, mucosa, or cornea) in any one stage (i.e. papule, vesicle, pustule, and/or scab[e]),

AND

In a vaccinee:

- The lesion is at an anatomical site(s) other than the vaccination site, *AND*
- Onset of the papule(s) is 0–28 days post vaccination, *OR*

If the patient has not received smallpox vaccination:

- Onset of the papule(s) is 0–28 days post exposure to vaccinia virus.

Exclusion criterion for all levels of diagnostic certainty

- An eruption that meets the Brighton Collaboration case definition of generalized vaccinia, eczema vaccinatum, or progressive vaccinia.[j]

Exclusion criteria for levels 2 and 3 of diagnostic certainty

- An etiologic agent other than vaccinia virus has been detected from the lesion(s) in question, *OR*
- The eruption resolves within 2–3 days of its onset, *OR*
- Histopathology, if available, is not consistent with the presence of vaccinia virus.

Notes for inadvertent inoculation case definition

Note: Refer to the full document for the guidelines and appendices mentioned in notes below.

a. Attention: With a history of eczema, atopic dermatitis or Darier's disease (keratosis follicularis), refer to the Brighton Collaboration case definition of eczema vaccinatum. If the criteria of level 1, 2, or 3 of diagnostic certainty of EV are not met, return to this case definition.

b. Review of all criteria (inclusion AND exclusion) prior to categorization of a case is necessary. All criteria (inclusion and exclusion) apply to the time of diagnosis.

c. Usually, a single lesion that is similar in appearance to that of an inoculation site, but can be at multiple sites and does not meet the definition of generalized vaccinia, eczema vaccinatum or progressive vaccinia.

d. For more detailed information on laboratory testing for vaccinia virus, see Appendix A.

e. A scab may not develop if the vaccination site is covered; rather a flaccid dark layer of skin that eventually comes off with the dressing may develop.

f. Mucosal sites like the oral mucosa will unlikely promote crusting of a lesion. It is likely that the lesion will remain as a mucosal ulcer and fill in but that any incipient scab/crust will not adhere or will be washed away.

g. Conjunctival lesions may not have a scab prior to resolution.

k. Expert is defined as a health-care provider, typically an ophthalmologist, knowledgeable in identifying vaccinia keratitis lesions.

i. Corneal lesions may present as grey-appearing superficial punctate keratitis that may later coalesce to form a geographic epithelial defect resembling herpes simplex keratitis. Stromal corneal lesions may present as small subepithelial opacities resembling epidemic keratoconjunctivitis that may be associated with epithelial defects and progress to corneal haze/clouding.

j. Whether these events (EV, PV, or GV) occur in vaccinated or nonvaccinated persons, they should be reported and analyzed as EV, PV, or GV. Additionally, during data analysis, the frequency of inadvertent inoculation should be adjusted to include these cases, so as not to underestimate the risk of inadvertent inoculation.

4.1.24 Progressive vaccinia (PV) following exposure to vaccinia virus (34)

For all levels of diagnostic certainty

PV lesions are typically concentrated at the site of vaccination with or without metastatic lesions and in severe cases may involve the entire body. Depending on the degree of immunosuppression vaccinia virus lesions may slowly progress over days to months with little surrounding inflammatory response if untreated and secondary infection is absent. Lesions persist after exposure until intervention measures are undertaken.

Symptoms or signs of a systemic viral illness, such as fever [≥38°C (≥100.4°F)][a], malaise and prostration, and localized edema or erythema are usually absent until the vaccinee is near death. Death occurs from toxemia either from viremia or septicemia due to secondary bacterial infection.

Level 1 of diagnostic certainty

- Laboratory evidence of cell-mediated immunodeficiency[b] or a documented clinical diagnosis of a disease that is known to be associated with cell-mediated immunodeficiency,

AND

- Primary lesion with failure to heal[c] and/or with progression to necrosis,

AND

- Laboratory confirmation (positive vaccinia virus-specific polymerase chain reaction or culture)[d] of vaccinia virus infection.

Level 2 of diagnostic certainty

- Laboratory evidence of cell-mediated immunodeficiency[b] or a documented clinical diagnosis of a disease that is known to be associated with cell-mediated immunodeficiency, *OR*
- Histopathologic confirmation[e] of weak or absent inflammatory response to the continuing spread of vaccinia virus,

AND

- Primary lesion with failure to heal[c] and/or with progression to necrosis,

AND

- Histopathology compatible with orthopox virus infection, and
- Laboratory evaluation for orthopox viruses[f] other than vaccinia, and for other causes of papular or vesicular eruptions[g] was performed and found to be negative.

Level 3 of diagnostic certainty

- A person recently vaccinated or known to be a close contact of a recent vaccinee[h],

AND

- Laboratory evidence of cell-mediated immunodeficiency[b] or a documented clinical diagnosis of a disease that is known to be associated with cell-mediated immunodeficiency, *OR*
- Histopathologic confirmation[e] of weak or absent inflammatory response to the continuing spread of virus,

AND

- Primary lesion with failure to heal[c] and/or with progression to necrosis.

Notes for progressive vaccinia case definition

Note: Refer to the full document for the guidelines and appendices mentioned in notes below.

a. See the Brighton Collaboration's case definition and guidelines for fever as an adverse event following immunization at: https://brightoncollaboration.org/public.
b. Laboratory-documented evidence of qualitative or quantitative evidence of dysfunction of the cell-mediated immune response. See Appendix A.
c. Although it is difficult to establish a time line, typically "failure to heal" refers to deviation from the normal progression at the vaccination site.
d. For more detailed information on laboratory testing for vaccinia virus, see Appendix B.
e. A biopsy of the margin of the area of necrosis in defective cell-mediated response will show apoptosis of cytotoxic T-cell populations and lysis of virus-containing cells. Marked infiltration by neutrophils and bacteria suggests secondary infection.
f. Laboratory testing for monkeypox or cowpox or variola is only indicated if recently in endemic area or history of contact with infected animals or persons.
g. Other papulo-vesicular conditions include: herpes simplex, varicella, rickettsialpox, scabies, drug eruptions, and allergic/contact dermatitis, mycoplasma pneumonia; see a list of infectious and non-infectious conditions in: 2nd edition of Long, Pickering, Prober: Principles and Practice of Pediatric Infectious Diseases, p. 436.
h. Examples of close contact would include direct (touching, sexual activity, or close contact sports activities) or (rarely) indirect (via shared bedding, clothing, wash cloths, inadequately sterilized medical devices, etc.) contact.

4.1.25 Robust take[a] following exposure to vaccinia virus (35)

The development of findings with the following characteristics (all of the following):

Level 1 of diagnostic certainty

- Erythema; *AND*
- Induration;

AND

- Tenderness; *OR*
- Warmth;

AND

- Erythema or induration is >7.5 cm in diameter; *AND*
- Begins to resolve within 72 h of onset with or without treatment; *AND*
- Occurs 8–12 days post-vaccination.

Level 2 of diagnostic certainty

- Erythema; *OR*
- Induration;

AND

- Tenderness; *OR*
- Warmth;

AND

- Erythema or induration is >7.5 cm in diameter; *AND*
- Begins to resolve within 72 h of onset with or without treatment *AND*
- Occurs 8–12 days post-vaccination.

Level 3 of diagnostic certainty

- Erythema; *OR*
- Induration;

AND

- Erythema or induration is >7.5 cm in diameter; *AND*
- Begins to resolve within 72 h of onset with or without treatment; *AND*
- Occurs 8–12 days post-vaccination.

Exclusion criterion for all levels of diagnostic certainty

- Fulfillment of the Brighton Collaboration[b] criteria for cellulitis or abscess at vaccination site.

Notes for robust take case definition

a. Review of all criteria (inclusion AND exclusion) prior to categorization of a case is necessary. All criteria (inclusion and exclusion) apply to the time of diagnosis.

b. See the Brighton Collaboration's case definitions for cellulitis and abscess at: https://brightoncollaboration.org/public.

4.2 General guidelines

Guidelines for the collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies (*36*) and in surveillance systems (*37*) have been developed by the Brighton Collaboration through a process similar to that described for AEFI-specific case definitions. Those guidelines were also reviewed and endorsed by this CIOMS/WHO Working Group and are reproduced, with the permission of the Brighton Collaboration, in Annexes 6 and 7.

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5

Methods to enhance the application of Brighton Collaboration case definitions

The Brighton Collaboration case definitions for AEFIs are disseminated to the scientific community working in the areas of vaccines and vaccination through publication in the journal *Vaccine*. These publications are available free of charge on the website of the Brighton Collaboration (https://brightoncollaboration.org/public).

The Brighton Collaboration case definitions have been developed to facilitate collecting and comparing data from clinical trials, epidemiological studies and surveillance systems. It is therefore important to disseminate the case definitions widely to all those designing such studies and systems as well as to those collecting and analysing the data. It is recognized that vaccine and health-care providers reporting AEFIs within passive surveillance systems (e.g. spontaneous reporting of AEFIs) may not be aware of the Brighton Collaboration case definitions, or indeed may not find most of the case definitions applicable to the reporting of suspected cases in settings with limited resources and diagnostic capacity. However, the criteria provided by a case definition may nevertheless be applied by those analysing the data. For this purpose, case definitions have been used during the review of reports of AEFIs in individuals for confirming the specific events reported and for classifying them according to the level of diagnostic certainty. A broader awareness of the Brighton Collaboration case definitions within the scientific community may be reached in the future through local and international training initiatives.

In order to enhance the application of Brighton Collaboration case definitions in clinical trials, epidemiological studies and surveillance systems, the CIOMS/WHO Working Group on Vaccine Pharmacovigilance identified three conditions to be fulfilled:

- Availability of the case definitions in other languages (see section 5.1);
- Compatibility of the case definitions with MedDRA (see section 5.2); and
- Reference to the case definitions in regulatory guidance documents (see section 5.3).

Further to the deliberations by the Working Group on ways to enhance the application of Brighton Collaboration case definitions, the industry representatives on the Working Group implemented a survey to determine if and how the case definitions are applied in clinical trials and which obstacles for their use may have to be overcome in the future; the report of this survey is summarised in section 5.4 below.

5.1 Translation of Brighton Collaboration case definitions

Significant efforts have been made by the Brighton Collaboration and its partners to ensure accessibility to its case definitions and related guidance documents through publication in the journal *Vaccine* and on the Brighton Collaboration website without paid subscription. Such access is critical to the use of the case definitions by pharmacovigilance stakeholders across different regions and settings. This CIOMS/WHO Working Group on Vaccine Pharmacovigilance included in its terms of reference to contribute to the dissemination and use of Brighton Collaboration case definitions through means such as supporting their translation into additional languages.

The Working Group agreed on the importance of having the case definitions available in multiple languages (particularly widely used languages). However, this objective was constrained by the resources that would be required to achieve full translation of all the case definitions. The first six published Brighton Collaboration case definitions (those for *Acute intussusception*, *Fever*, *Generalized convulsive seizures*, *HHE*, *Nodule at injection site* and *Persistent crying)* have been previously translated in full into Spanish and French with WHO support and are available through the Brighton Collaboration website at https://brightoncollaboration.org/public. The feasibility of using several avenues for additional translation was explored by this Working Group. Ultimately it was decided that, given the resources available, the most feasible approach was a translation of the core case definition with an accompanying introduction (see Annex 5) and abridged preamble. A sample of five published case definitions was selected for translation in this format. In doing so a number of issues were discussed, including the variability in case definitions both in their content as well as their anticipated use. While some definitions (e.g. those for *Aseptic meningitis* and *Abscess*) are relatively straightforward and easy to translate, others (e.g. that for *Encephalitis, myelitis and acute disseminated encephalomyelitis*) are not. Case definitions like that for encephalitis are extensive and judgment is required as to how to come up with abridged translations without losing key information or meaning. It is important to state, however, that the selection of this sample was in no way intended by the Working Group to designate specific case definitions as most important among all the Brighton Collaboration case definitions. Translations of the five abridged case definitions into French and Portuguese were completed with

in-kind support from two participating agencies in the Working Group, the Public Health Agency of Canada and the Brazilian National Health Surveillance Agency respectively.

The case definitions translated were *Abscess at injection site*; *Aseptic meningitis*, *Cellulitis at injection site*; *Encephalitis, myelitis, and acute disseminated encephalomyelitis* and *HHE*. In addition, the general guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies and in surveillance systems were translated in their entirety. The abridged case definitions in English are available through the Brighton Collaboration website (https://brightoncollaboration.org/public) for use by other groups seeking to translate them into other languages. Such translations should be done in conjunction with the Brighton Collaboration to ensure consistency and validation of translations. The French and Portuguese versions are also provided through the Brighton Collaboration website.

The translations were reviewed and validated by this Working Group (i.e. reviewed for scientific and technical accuracy in the second language), however they were not validated by the original Brighton Collaboration case definition working groups due to lack of the specific language expertise. Thus the translations are provided by this Working Group for convenience and should not be seen as modifying the original case definitions in any way. The Working Group encourages users to always refer to the original English case definitions, particularly if there is any question of doubt about the translated versions.

Gaps remain in the dissemination, and consequently use, of Brighton Collaboration case definitions in other languages than English. Thus, the Working Group encourages the translation of more case definitions into additional languages in the future. Given the similarities in some terms across case definitions, it would be desirable to have a glossary of translated terms as a core technical resource to further enhance vaccine pharmacovigilance and for use in future translations. A glossary could also become a useful resource in light of existing differences in interpretation of terms in English usage in various regions.

5.2 Mapping of terms: MedDRA and Brighton Collaboration case definitions

At the inception meeting of the Working Group, the potential for interaction between the terms defined by the Brighton Collaboration and other standard terminology for reporting adverse event information such as Med-

DRA was recognized. Thus the terms of reference for the CIOMS/WHO Working Group on Vaccine Pharmacovigilance included collaboration with the CIOMS Working Group on SMQs. It also stated that the Working Group on Vaccine Pharmacovigilance would provide input on SMQs in development to allow application to vaccines, and suggest additional SMQs for development, particularly those applicable to vaccines. To address this term of reference, the Working Group established a MedDRA Mapping Subgroup[1] at its November 2006 meeting.

MedDRA is a medical terminology developed by the ICH[2] and used "to classify adverse event information associated with the use of biopharmaceuticals and other medical products (e.g. medical devices and vaccines)"(*1*). MedDRA is used to code and report adverse event data from clinical trials, and for post-licensure reports and pharmacovigilance, and therefore enhances more ready exchange and analysis of data related to the safe use of medicinal products. It is maintained by the Maintenance and Support Service Organization (MSSO), which also serves as the repository and the source for the most up-to-date information regarding MedDRA and its application. The MSSO requires MedDRA subscribers to submit a Change Request for proposed additions, relocations, or modifications of MedDRA terms or SMQs. The proposal is accepted or rejected by an international panel of MSSO medical personnel.

SMQs are "groupings of MedDRA terms from one or more System Organ Classes that relate to a defined medical condition or area of interest. They are intended to aid in identification and retrieval of potentially relevant reports from a drug safety database." (*2*).

The MedDRA Mapping Subgroup started its work by comparing AEFI cases retrieved using the *Anaphylactic reaction SMQ* to those meeting the Brighton Collaboration *Anaphylaxis* case definition (in draft at that time) in both a regulatory authority and a manufacturer database.

Three types of SMQs were considered during the Subgroup's work on anaphylaxis terms. They are as defined by the CIOMS SMQ Working Group (2): (a) Narrow SMQs intended to capture only the cases most likely to represent the condition under review, (b) Broad SMQs intended to capture all possible cases, whilst possibly including some that may be irrel-

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[1] Unless otherwise specified, all references to "subgroup" in section 5.2 refer to the MedDRA Mapping Subgroup of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.

[2] MedDRA is the agreed terminology of data exchange with regulatory agencies in the European Union, Japan and the United States of America. There are other countries which also use MedDRA.

evant, and (c) Algorithmic SMQs useful for situations where a syndrome of clinical findings is likely to involve a collection of Preferred Terms (PTs) some of which are common to many other medical conditions. The Narrow SMQ did not adequately capture cases meeting the Brighton Collaboration case definition. The Broad SMQ, while useful as an initial screen, retrieved many cases that did not meet the Brighton Collaboration case definition. There was better concordance between the Algorithmic SMQ and the Brighton Collaboration case definition; however, differences resulted from variation in interpretation of reported events and coding.

This initial analysis resulted in improved clarity of language in the final Brighton Collaboration *Anaphylaxis* case definition, as well as a recommendation to the Brighton Collaboration that all draft Brighton Collaboration case definitions be reviewed for MedDRA coding prior to finalization. In addition, the exercise raised a number of questions to be addressed by the subgroup:

- What is the purpose of mapping Brighton Collaboration case definitions to MedDRA?
- Should all finalized Brighton Collaboration case definitions be mapped to MedDRA?
- What if there is an existing SMQ?
- Who will maintain and update the mapping with version and case definition changes?

The subgroup met regularly between 2007 and 2010 to address these questions. Subgroup activities are detailed under each question below.

5.2.1 Purpose of mapping Brighton Collaboration case definitions to MedDRA

Mapping concepts in Brighton Collaboration case definitions to MedDRA terms could facilitate database searches for adverse event reports meeting the respective Brighton Collaboration case definitions. Such a retrospective search (i.e. following report entry into the database) could be broad to fully capture all possible cases; however, subsequent manual case review would be necessary to identify cases truly meeting the case definition. The alternative would be a fully automated approach, using a narrower or algorithmic list of MedDRA terms. The subgroup did not consider a fully automated approach technically feasible for most Brighton Collaboration case definitions, which tend to be algorithmic and often include complex inclusion and exclusion criteria.

Prospectively flagging adverse event reports meeting the Brighton Collaboration case definition would eliminate variability in retrospective retrieval due to differences in coding conventions. The Brighton Collaboration case definition could be applied by the reporter at the time of the report, or during case processing. The Canadian AEFI report form (*3*) is a good example of this prospective approach. Prospective application of Brighton Collaboration case definitions might be feasible for select surveillance systems, but would be impractical for databases collecting spontaneous adverse event reports from a wide range of sources (e.g. VAERS).

Mapping Brighton Collaboration case definitions to MedDRA when they are still under development has the additional benefit of helping to refine the language in the case definition. The subgroup mapped drafts of the Brighton Collaboration *Diarrhea* and *Bell's Palsy* case definitions during their development. No changes to the Brighton Collaboration case definitions were recommended based on the mapping to MedDRA. A new SMQ was not felt to be warranted for either concept because certain important criteria in the case definitions (e.g. 3 or more bowel movements; liquid or semi-liquid consistency; reported within a 24-hour period; unilateral versus bilateral; sudden onset; rapid progression) are not captured in MedDRA terminology. While most cases of diarrhea would be retrieved by the High Level Term (HLT) *Diarrhea (excl infective)*, cases reporting only signs and symptoms of Bell's Palsy could be missed in a search based on coded terms. There are no suitable terms in MedDRA for decreased movement of the corner of the mouth and decreased movement of the forehead, and inadequate terms for decreased ability to close the eye and spontaneous or provoked movement of affected muscles. Since MedDRA generally does not include terms for a condition at each possible anatomic site, the subgroup did not consider a Change Request warranted in this case.

5.2.2 Mapping Brighton Collaboration case definitions to MedDRA

At the May 2007 meeting, the Working Group recommended mapping of select Brighton Collaboration case definitions (e.g. *Anaphylaxis*) to MedDRA terms. Definitions would be selected based on the likelihood that mapping could change the accuracy of recognition and reporting, and thereby improve management practices in some settings.

In May 2008, the Working Group communicated its plan regarding MedDRA mapping to the MedDRA Management Board and reported its discussions with the CIOMS Core SMQ Group regarding the potential for new SMQs. The MedDRA Management Board proposed that the MSSO map all

Brighton Collaboration case definitions to MedDRA PTs to assist this Working Group in identifying significant gaps. The MSSO subsequently mapped each concept in all of the published Brighton Collaboration case definitions to the best matched MedDRA PT. The MedDRA Mapping Subgroup of this Working Group reviewed the mapping and submitted a Change Request in February 2009, for new Lower Level Terms (LLTs) and PTs, as well as re-routing of certain LLTs and PTs. Some of the proposals in the Change Request were accepted, with or without modification, and implemented in MedDRA Version 12.1. The key reasons (as provided by the MSSO) why proposed new terms or re-routing of terms were not accepted are as follows:

- Multiple LLTs can be coded in a case, obviating the need for a new PT combining the concepts (e.g. using the LLT *Blood in stools* and LLT *Mucous stools* to capture bloody mucous stools).
- Certain terms are more appropriately placed as an LLT rather than a PT (e.g. *Persistent crying* under the PT *Crying*).
- Severity does not sufficiently differentiate concepts to justify a new PT (e.g. *Atonia* should remain an LLT under the PT *Hypotonia* rather than elevated to its own PT).

The MSSO had mapped each concept in the Brighton Collaboration case definition to the best matched MedDRA PT to identify gaps in MedDRA terminology. For the purposes of requesting a new SMQ or comparing terms to an existing SMQ, the subgroup broadened the mapping to include all possible PTs consistent with the concept in the Brighton Collaboration case definition.

At each meeting of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance, the Working Group reviewed published Brighton Collaboration case definitions and SMQs in production to decide if a request should be made for a new SMQ. Several Brighton Collaboration case definitions (e.g. *Diarrhea* and those for injection site reactions) were considered for SMQ development, but the utility of an SMQ was felt to be limited because of existing HLTs that could be utilized for a database search. Other Brighton Collaboration case definitions (e.g. *Intussusception*, *Unexplained sudden death in the first and second year of life*) were also considered for SMQ development, but were dependent upon laboratory testing for confirmation or exclusion, and specific laboratory test results are not routinely included in MedDRA terminology. The Working Group submitted a request to the MSSO in April 2009, for the development of a new SMQ for HHE, which was accepted for development by the CIOMS Core SMQ Group.

5.2.3 *Existing SMQ for same medical condition as Brighton Collaboration case definition*

At the October 2007 meeting, the Working Group discussed options if there is an existing SMQ for the same medical condition as the Brighton Collaboration case definition. While a few Brighton Collaboration case definitions (e.g. *HHE*) are primarily vaccine-specific, most Brighton Collaboration case definitions describe adverse events that can occur in association with any medicinal product. However, priorities for SMQ development might differ for vaccine versus non-vaccine products, as evidenced by the relatively few SMQs capturing concepts similar to those in the Brighton Collaboration case definitions.

The following SMQs were considered by the subgroup to capture concepts similar to those in Brighton Collaboration case definitions: *Anaphylactic reaction, Convulsions, Noninfectious encephalitis, Noninfectious meningitis, Guillain-Barré syndrome,* and *Thrombocytopenia*. Based on a comparison of PTs mapped from concepts in the Brighton Collaboration *Thrombocytopenia* case definition to PTs in the *Thrombocytopenia* SMQ, it was recognized that spontaneous bleeding terms in the case definition had been included in the *Haemorrhage terms (excluding laboratory terms)* SMQ rather than the *Thrombocytopenia* SMQ. While the Working Group considered requesting a new SMQ for spontaneous bleeding, it would be very difficult to construct such an SMQ since most MedDRA terms related to bleeding terms do not distinguish spontaneous from traumatic bleeding. PTs mapped from the concepts in the Brighton Collaboration *Generalized convulsive seizure* case definition focused primarily on signs and symptoms of generalized seizure, while PTs in the *Convulsions SMQ* included seizure disorder and epilepsy terms, as well as focal seizure terms. The Working Group therefore requested a new algorithmic sub-SMQ for generalized convulsive seizure in February 2010, which was accepted for development by the CIOMS Core SMQ Group.

Based on a comparison of PTs mapped from concepts in the Brighton Collaboration *Encephalitis, Anaphylaxis, and Guillain-Barré syndrome* case definitions to PTs in the respective SMQs, new terms derived from the Brighton Collaboration case definitions were proposed for addition to the SMQs. The terms will be tested by members of the CIOMS Core SMQ Group to determine if they should be added to the respective SMQs.

5.2.4 Maintenance of mapping with MedDRA version and Brighton Collaboration case definition changes

The subgroup recommended that new SMQs based on Brighton Collaboration case definitions, or revisions to existing SMQs for closer conceptual match to Brighton Collaboration case definitions, go through the development process delineated in the CIOMS Report on Development and Rational Use of Standardised MedDRA Queries (*4*). In this process, the MSSO updates each SMQ in production with each MedDRA version change. A Change Request could be submitted to the MSSO to modify an SMQ if significant changes are made to the Brighton Collaboration case definition upon which it is based.

The Working Group regularly collaborated with the MSSO and CIOMS Core SMQ Group. An International Medical Officer for the MSSO was a liaison member of this Working Group, and other members of the MSSO attended relevant sessions at Working Group meetings. In 2008 and 2009, the MedDRA Mapping Subgroup regularly updated and interacted with the CIOMS Core SMQ Group at core group meetings. Outcomes from these meetings are summarized below.

- May 2008 – The CIOMS Core SMQ Group agreed to test four SMQs (*Noninfectious meningitis, Guillain-Barré syndrome, Convulsions*, and *Anaphylactic reaction*) on vaccine databases.
- September 2008 – The CIOMS Core SMQ Group and the subgroup representative proposed collaborative comparative testing of the SMQ and Brighton Collaboration case definition (with standardized methodology) for the following concepts: *Noninfectious meningitis, Guillain-Barré syndrome, Convulsions*, and *Anaphylactic reaction*. Prior to any testing on databases, the MedDRA Mapping Subgroup would map the concepts in the Brighton Collaboration case definition to MedDRA PTs and compare PTs between the Brighton Collaboration case definition and SMQ.
- March 2009 – An update on subgroup activities was presented, including a decision to focus the term comparisons on *Anaphylaxis, Convulsions, Thrombocytopenia*, and *Guillain-Barré syndrome*.
- September 2009 – An update on subgroup activities was presented, including the results of mapping the Brighton Collaboration *Diarrhea, Injection site reaction, Thrombocytopenia*, and *Convulsions* case definitions. The CIOMS Core SMQ Group agreed that new

SMQs for diarrhea and injection site reaction were unnecessary, given available HLTs in MedDRA, and that a Spontaneous Bleeding SMQ would not be feasible. The CIOMS Core SMQ Group supported the concept of a sub-SMQ for generalized convulsive seizure.

The need to assess SMQ performance during the period of administration of pandemic influenza A/H1N1 vaccines, review new or updated Brighton Collaboration case definitions for coding purposes, and evaluate other terminology systems (e.g. WHO-ART, International Classification of Diseases-10 (ICD-10)) for application to vaccines provides a strong rationale for continuing the work of the MedDRA Mapping Subgroup beyond the tenure of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Future work will be conducted under the auspices of the Brighton Collaboration.

5.3 Reference to Brighton Collaboration case definitions in guidance documents

The following is a list of examples (not intended to be exhaustive) of references to Brighton Collaboration case definitions in guidance documents and other vaccine pharmacovigilance resources:

5.3.1 Global initiatives

- The awareness of the Brighton Collaboration case definitions and potential for their use has gradually been increasing worldwide in the past five years. In part this has been due to efforts by WHO and other agencies to promote their use through vaccine safety training workshops. The case definitions are also more regularly used in the review of reports of AEFIs in individuals, in particular in the investigation and assessment of serious AEFIs for validation and classification of the event reported according to the level of diagnostic certainty.

5.3.2 Regional and country initiatives

- European Union: The guideline *Conduct of Pharmacovigilance for Vaccines for Pre- and Post-Exposure Prophylaxis Against Infectious Diseases* and the guidelines on influenza vaccines referred to in Volume 9A of *The Rules Governing Medicinal Products in the European Union* (*5*) encourage the use of the Brighton Collaboration case definitions and refer to this Working Group report.

- Region of the Americas: the Brighton Collaboration case definition for *Acute intussusception* has been used for post-licensure monitoring of rotavirus vaccines, in particular by a network of countries established in 2006 (the "SANEVA" network) linked to the early introduction of rotavirus vaccines for routine use in the region (*6*).
- Brazil: the Brighton Collaboration case definitions for *Anaphylaxis* and *Guillain-Barré syndrome* were included in the *Protocol for Epidemiological Surveillance of Adverse Events Following Immunization – Vaccination Strategy against Pandemic Influenza Virus (H1N1)*. (*7*). This orientation was provided for health-care providers at all levels in the country when dealing with a suspected AEFI. At the central level the case definitions are applied as additional diagnostic evaluation for serious AEFI cases by the Agência Nacional de Vigilância Sanitária (ANVISA, the Brazilian Health Regulatory Agency) and the Coordenação Geral do Programa Nacional de Imunizações/Ministério da Saúde (CGPNI/MS, the Brazilian Immunization Programme).
- Canada: The national AEFI case definitions have been based, where possible, on the Brighton Collaboration case definitions, as noted in Appendix 3 of the *User Guide: Report of Adverse Events Following Immunization (AEFI)* (*8*).
- US: Guidance issued by the US Food and Drug Administration, in particular the *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* (*9*), makes reference to the Brighton Collaboration case definitions. Also, the American Academy of Pediatrics, in the *Report of the Committee on Infectious Diseases* issued in 2009 (*10*), refers to the Brighton Collaboration case definitions as facilitating sharing and comparison of vaccine data worldwide.

5.4 Industry survey on use of Brighton Collaboration case definitions

A survey of vaccine manufacturers' representatives was conducted in 2009-2010 to identify aspects of the Brighton Collaboration case definitions and guidelines that are helpful for the collection, analysis and presentation of safety data in clinical studies, as well as obstacles that need to be addressed to improve their use. The survey was sent to 60 industry representatives, 20 via the International Federation of Pharmaceutical Manufac-

turers & Associations (IFPMA) and 40 to the members of the Developing Countries Vaccine Manufacturers Network.

The response rate was low (17%) and a majority of the responders were representatives of developing country vaccine manufacturers (8 of 10 responders) compared to representatives of industrialized country vaccine manufacturers (2 of 10 responders). Another 20 representatives opened the online survey but did not complete it.

Among responders who reported that they used the Brighton Collaboration case definitions and guidelines in clinical studies, the case definitions for *Swelling at or near injection site* and *Induration at or near injection site* were the most frequently applied case definitions for data collection, analysis and presentation of local reactions in clinical trials (8 and 7 responders, respectively) while that for *Cellulitis at injection site* was the least frequently used (5 responders). For general systemic events, the case definition for *Fever* was the most frequently used (8 responders) and that for *Fatigue* was the least frequently used (5 responders). The percentage of use of the case definitions for neurologic conditions was lower than for local reactions and general systemic events; the case definition for *Generalized convulsive seizures* was the most frequently used with only 5 responders indicating its use for data collection and 3 for data analysis and presentation while the case definition for *Encephalitis, myelitis, and acute disseminated encephalomyelitis* was cited for data collection by only one responder. A similar rate of use was reported for case definitions of vaccinia-related events, which can be explained by the reduced number of clinical trials with this vaccine.

Two out of the 10 responders did not use the Brighton Collaboration case definitions and guidelines for clinical trials. The reasons for not using them were as follows:

- lack of knowledge of their existence,
- alternate case definitions are available from regulatory authorities or immunization programmes or within the company, and
- the guidelines are too complicated

Responders also noted that some terms like extensive limb swelling and apnoea have not been defined by the Brighton Collaboration and required other references. Lastly, suggestions were made for case definitions for future development, namely for syncope, anaphylactoid reaction and viscerotropic disease.

Given the overall low response rate of the current survey, the results should not be considered as representative or applied generally. However, they do provide preliminary useful information about the pattern of use of Brighton Collaboration case definitions for AEFIs by the vaccine industry. The CIOMS/WHO Working Group on Vaccine Pharmacovigilance concluded that the need to explore further the awareness of and the practicality of use of those case definitions provides a strong rationale for continuing this exercise beyond the Working Group's tenure with improvements to the survey methodology in order to increase the response rate. Similar surveys may also be considered for other stakeholders who are potential users of those case definitions. Possible improvements to the survey could include revising the survey instrument, survey delivery, interviews of focus groups, and collaboration with the Brighton Collaboration in conducting the survey.

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6

Conclusions and future directions

6.1 Practical use of the outputs of the Working Group

It is anticipated that stakeholders will utilise the outputs of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance in a variety of settings to enhance vaccine pharmacovigilance. In addition to this report, the outputs of the Working Group will be disseminated through web links, publications, technical resources and training materials.

The *Vaccine pharmacovigilance* definition (Section 3.1) and *AEFI general definitions* (Section 3.3) can be used to strengthen the application of pharmacovigilance standards and terminology in AEFI surveillance systems. The new definitions can be applied by WHO and other public health agencies, regulatory authorities, the vaccine industry, and researchers when they develop or update recommendations or guidelines on vaccine pharmacovigilance activities, including updates to previously utilized terms. They may also facilitate implementation of vaccine pharmacovigilance processes and better identify vaccine-related components to be specifically addressed. The proposed terminology will facilitate communications and exchange of information on vaccine safety between regulatory authorities worldwide and with industry and other stakeholders.

The *Vaccination failure* discussion (Section 3.2) forms the basis for development of vaccine-specific definitions of failure, which could be used for classification of individual cases and in the review of vaccination failure in PSURs and other aggregate data reports in the future. In addition, the concepts discussed can support vaccine effectiveness studies and other investigations.

The *Points to consider regarding differences between vaccines and drugs in signal detection* (Section 3.4) enhance vaccine pharmacovigilance by providing a better understanding of signal detection, evaluation, and management in the vaccine and vaccination contexts.

Endorsement of Brighton Collaboration case definitions by this Working Group should improve their acceptance and use in a variety of settings by multiple stakeholders. Working Group members from regulatory agencies encourage their use through regulatory guidance documents and discussions with the vaccine industry. The Canadian AEFI report form (*1*) and follow-up forms sent to AEFI reporters in Brazil (Personal communication, M. Freitas Dias) are good examples of the prospective application of Brigh-

ton Collaboration case definitions as is the use of those case definitions in clinical and epidemiological studies (*2*). Future translation of Brighton Collaboration case definitions, as well as the translation of the general vaccine pharmacovigilance definitions by this Working Group, will broaden access to these resources and enhance their use.

The Working Group conducted a survey of industry on the use of Brighton Collaboration case definitions in clinical studies (Section 5.4). Follow-up on this survey, as well as additional surveys of other stakeholders, will help to identify obstacles and improve the use of Brighton Collaboration case definitions.

Based on a recommendation from this CIOMS/WHO Working Group, Brighton Collaboration working groups should now routinely consider MedDRA mapping during case definition development. New vaccine-specific terms proposed by the CIOMS/WHO Working Group and added to MedDRA by the MSSO, should improve the coding of vaccine reports and their retrieval from vaccine databases. In addition, the development of new SMQs and modification of existing SMQs based on Brighton Collaboration case definitions, should improve the ability to retrieve AEFI cases from regulatory agency, industry and other databases.

The 2009-2010 influenza A/H1N1 pandemic highlighted the importance of the outputs of this Working Group. Prior to the pandemic, adverse events of special interest were defined by many regulatory authorities worldwide in order to focus pharmacovigilance activities in the context of a mass vaccination campaign. In the European Union, guidelines were issued with recommendations for the use of the MedDRA terminology (PTs and SMQs) as a common tool for retrieval of relevant terms in databases of spontaneous reports, including EudraVigilance, and of Brighton Collaboration definitions, where available, for case classification. More specifically, Narrow SMQs were applied for anaphylaxis (using a combination of the SMQ for *Anaphylactic reaction* and the SMQ for *Angioedema*), *Convulsions*, *Demyelination, Guillain-Barré syndrome, Neuritis and Non-infectious encephalitis*, and MedDRA PTs for *Facial palsy* and *Vasculitis*. SMQs proved especially useful to capture reports of heterogeneous clinical conditions like demyelinating disorders and of complex neurological disorders with clinical variants, such as GBS. During the pandemic, weekly or bi-weekly exchange of information on signals between regulatory authorities proved to be a critical step to quickly identify and evaluate potential safety issues and communicate with the

public on safety issues. The Brighton Collaboration case definitions facilitated this exchange of data by providing a common language summarising case descriptions and allowing for the provision of the number of cases of the same levels of diagnostic certainty in each country or jurisdiction. This experience with influenza A/H1N1 vaccine pharmacovigilance illustrates the need for harmonized case retrieval tools and case definitions. It is hoped that continued endorsement of such harmonized case definitions, such as those of the Brighton Collaboration, by a scientific working group including representatives of various stakeholders active in vaccine pharmacovigilance will facilitate their dissemination and implementation.

6.2 Gaps and future directions

Monitoring vaccine safety is a shared responsibility among different stakeholders. Current advances in vaccine research and development, prelicensure evaluation and post-licensure monitoring as well as advances in medical and information technologies are creating opportunities to further enhance immunization safety globally.

In this publication, the CIOMS/WHO Working Group on Vaccine Pharmacovigilance reports on work achieved to date and proposes possible solutions for further improving the tools to enhance the performance of vaccine pharmacovigilance. The initial premise of this Working Group was to give support to the evolving need of a harmonized view on terms and case definitions used in pharmacovigilance. The challenge faced by industry, regulatory agencies, academia and public health agencies to agree on critical aspects of these essential tools was one of the driving forces behind the group's initiation. Endorsement of Brighton Collaboration case definitions and activities to encourage their use represent the clearest examples of the benefits from this joint effort. Over the course of the Working Group's tenure, use of these standard definitions by participating agencies and companies has increased both for post-licensure surveillance and in the monitoring of clinical trials. Working Group members appreciate that by facilitating the harmonization and increasing the possibility to compare data from different clinical studies and health-care systems, the Brighton Collaboration case definitions contribute to improving methodologies and global analyses of signals in vaccine pharmacovigilance hence promoting understanding of the safety of different vaccines in different populations.

It is anticipated that stakeholders such as those represented in this Working Group will use the outcome of the work in a variety of settings to enhance vaccine pharmacovigilance. The discussion above on *Practical Use of the Work of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance* illustrates the relevance of this work in those situations. Vaccine pharmacovigilance and AEFI general definitions will help strengthen the application of pharmacovigilance standards and terminology to AEFI surveillance systems. This, in turn, will facilitate the work of WHO and other public health agencies in developing practical guidelines and will support regulatory agencies, industry, academia and other institutions with vaccine-specific pharmacovigilance activities. The new terminology will also facilitate exchange of information between stakeholders.

Milestones identified in the business plan of this Working Group have been met and the goal of this consensus work has been achieved. However, the proposed tools will require revision over time, on the basis of new experience gained from their implementation and also taking into account evolving methodologies. As new challenges will be faced continuously, there would be a need for maintaining a forum where harmonized approaches can be developed for the public and private sectors in ensuring the safety of vaccines. A number of solutions have been identified for continuing some of the activities initiated by the Working Group: the Brighton Collaboration is undertaking further translations of its case definitions as well as the mapping of MedDRA terms to those in its case definitions. In addition, the Working Group may be convened on an ad hoc basis to review future Brighton Collaboration case definitions.

A possible role for a similar Working Group after publication of this report has been discussed amongst members of the current Working Group. The current Global Vaccine Safety Blueprint Project, led by a Collaborative Group supported by WHO, is exploring the broad area of capacity development for vaccine safety in low- and middle-income countries. A global support network for this blueprint project would certainly benefit from a discussion forum where regulators and industry can join forces in refining their common methodological approaches. The CIOMS/WHO Working Group on Vaccine Pharmacovigilance, composed of senior scientists from vaccine industry, regulatory agencies, governmental institutions and academia, has comprised a unique body of competence and it would be regrettable not to take further advantage of this. The general opinion of the Working Group is that if a group can proactively continue to work with

harmonization of terminology and other tools within vaccine pharmacovigilance, this will save time and costs for all parties.

The field of vaccine safety generates increasing interest and diverse activities. Although other efforts between the vaccine industry and regulatory agencies to enhance the impact of their respective efforts in monitoring vaccine safety and managing risks are underway, there is a need for a forum that would include the broadest possible representation of regulators from all parts of the world as well as a broad collection of multinational companies together with manufacturers from emerging economies and representatives from relevant public health institutions and academia. A brief catalogue of areas that could benefit from common approaches would include in particular:

- Continued development of post-licensure approaches to pharmacovigilance. This includes, amongst other reporting and data-collection methods, traditional pharmacovigilance, epidemiological methods, assessment of benefits and risks and communication related to those, the use of computerized medical records and text-mining, including analytic dimensions such as coding conventions and development of algorithms to help clinicians manage AEFI cases.
- A rapidly developing field of risk management plans, potential risk mitigation activities and risk communication strategies for how to respond to vaccine safety concerns in a timely manner.
- Global capacity building development, in particular in relationship with the growing needs for vaccine pharmacovigilance when new vaccines are being introduced or during mass vaccination campaigns.
- Pre-licensure safety monitoring in clinical trials, including the assessment of new vaccine technology and additives such as adjuvants and preservatives as well as the application of Brighton Collaboration case definitions of AEFIs (where available) and their general guidelines.

Should a similar group be assembled again, and depending on the scope of work retained, the group's composition could be reviewed. A different profile of expert knowledge, new membership with complementary expertise or representing additional bodies not previously included should also be considered.

The scope of vaccine safety activities has expanded during the tenure of this Working Group. There are newer pharmacovigilance methods that offer the possibility of more immediate, effective and accurate analyses of safety signals and an increased potential to better investigate the causality of AEFIs. There are also more sophisticated regulatory requirements that take advantage of developing information technologies and anticipate the occurrence of vaccine safety issues. There is a greater understanding of the importance of properly communicating with a broad range of stakeholders about risks that are associated with the use of vaccines and how those can be minimized. Continuously improving these methods will require diligence, innovative thinking, and hard work and would certainly benefit from the establishment of a new body modelled after some of the successful principles that contributed to the achievements of this Working Group.

References

1. *Adverse Events Following Immunization Reporting Form*. Public Health Agency of Canada, (http://www.phac-aspc.gc.ca/im/aefi-form-eng.php accessed 24 February 2011).
2. Buettcher M et al. Three-year surveillance of intussusception in children in Switzerland. *Pediatrics*, 2007, 120:473-480.

Annex 1

Membership and meetings of the Working Group

The CIOMS/WHO Working Group on Vaccine Pharmacovigilance met in a series of 11 meetings from November 2005 through October 2010. This Working Group report was reviewed in draft form by participating members at its final meeting in October 2010 and finalized thereafter for publication. The members of the Editorial Group were: P Bahri, A Bentsi-Enchill (Chief Editor), M Blum, U Heininger, E Matos dos Santos and G Sjölin-Forsberg.

During the course of its work, the Working Group recognized its membership to represent the following broad groups of stakeholders (or interested parties) in vaccine pharmacovigilance: vaccine regulatory authorities; vaccine industry; and national and international public health agencies and academia. Members, their institutional affiliations and stakeholder groups (as defined above) as well as a chronological summary of the Working Group meetings are listed below.

Name	Organization (Stakeholder group)*	Duration of membership**
Novilia Sjafri Bachtiar	PT Bio Farma *(Vaccine industry)*	Partial
Priya Bahri	European Medicines Agency *(Vaccine regulatory authorities)*	Full
Steve Bailey	Pfizer *(Vaccine industry)*	Partial
Robert Ball	US Food and Drug Administration *(Vaccine regulatory authorities)*	Partial
Adwoa D Bentsi-Enchill	World Health Organization	Full
Michael Blum	Wyeth Research, Pfizer *(Vaccine industry)*	Full
Miles Braun	US Food and Drug Administration *(Vaccine regulatory authorities)*	Partial
Patrick Caubel	Sanofi Pasteur *(Vaccine industry)*	Partial
Adrian Dana	Merck & Co., Inc. *(Vaccine industry)*	Full
Alex NO Dodoo	University of Ghana Medical School *(Public health agencies and academia)*	Full
Philippe Duclos	World Health Organization	Partial

Name	Organization (Stakeholder group)*	Duration of membership**
John Ferguson	Novartis *(Vaccine industry)*	Partial
Murilo Freitas Dias	Agência Nacional de Vigilância Sanitária – ANVISA (Brazil) *(Vaccine regulatory authorities)*	Full
Jane Gidudu	US Centers for Disease Control and Prevention *(Public health agencies and academia)*	Partial
Katharina Hartmann	Crucell/Berna Biotech Ltd *(Vaccine industry)*	Partial
Ulrich Heininger	*University Children's Hospital, Basel (Switzerland) (Public health agencies and academia)*	Full
Renald Hennig	Chiron Vaccines *(Vaccine industry)*	Partial
Juhana E Idänpään-Heikkilä	CIOMS (Senior Adviser, Past Secretary-General)	Partial
John Iskander	US Centers for Disease Control and Prevention *(Public health agencies and academia)*	Partial
Patrizia Izurieta	GlaxoSmithKline Biologicals *(Vaccine industry)*	Partial
Suresh S Jadhav	Serum Institute of India Ltd *(Vaccine industry)*	Full
Douglas Kargman	Novartis Vaccines and Diagnostics *(Vaccine industry)*	Partial
Brigitte Keller-Stanislawski	Paul-Ehrlich-Institut *(Vaccine regulatory authorities)*	Full
Katrin Kohl	US Centers for Disease Control and Prevention *(Public health agencies and academia)*	Partial
Gottfried Kreutz	CIOMS (Past Secretary-General)	Partial
Xavier Kurz	European Medicines Agency *(Vaccine regulatory authorities)*	Full
Barbara J Law	Public Health Agency of Canada *(Public health agencies and academia)*	Full
Elizabeth Loupi	Sanofi Pasteur *(Vaccine industry)*	Partial
Eliane Matos dos Santos	Bio-Manguinhos/FIOCRUZ *(Vaccine industry)*	Partial
Reinaldo de Menezes Martins	Bio-Manguinhos/FIOCRUZ *(Vaccine industry)*	Partial
Shanthi Pal	World Health Organization	Partial
Mair Powell	Medicines and Healthcare Products Regulatory Agency (UK) *(Vaccine regulatory authorities)*	Partial
Jerome Premmereur	Novartis *(Vaccine industry)*	Partial
Eva-Beate Rump	MSSO (MedDRA) liaison member	Partial

Name	Organization (Stakeholder group)*	Duration of membership**
Harry Seifert	GlaxoSmithKline Biologicals *(Vaccine industry)*	Partial
Harry Kartini Setyaningsih	PT Bio Farma *(Vaccine industry)*	Partial
Françoise Sillan	Sanofi Pasteur *(Vaccine industry)*	Partial
Gunilla Sjölin-Forsberg	CIOMS (Secretary-General, 2010 to present)	Partial
Theodore Tsai	Novartis *(Vaccine industry)*	Partial
Patrick Zuber	World Health Organization	Partial

* At the time of membership on the Working Group.

** "Partial" denotes membership in the Working Group for a portion of the 5-year period while "Full" denotes membership for the full period.

Time and location of Working Group meeting	Host***
November 2005 (Geneva)	World Health Organization
May 2006 (Langen)	Paul-Ehrlich-Institut
November 2006 (Brussels)	GlaxoSmithKline Biologicals
May 2007 (Geneva)	International Federation of Pharmaceutical Manufacturers & Associations
October 2007 (Bethesda)	US Food and Drug Administration
May 2008 (London)	European Medicines Agency
October 2008 (Ottawa)	Public Health Agency of Canada
May 2009 (Zurich)	Crucell
October 2009 (Atlanta)	US Centers for Disease Control and Prevention
April 2010 (Lyon)	Sanofi Pasteur
October 2010 (New York)	Pfizer

*** Costs for travel and accommodation were covered by each Working Group member's parent organization or by CIOMS as per rules, and were not covered by meeting hosts.

Annex 2

Selected CIOMS publications

- Safety Requirements for the First Use of New Drugs and Diagnostic Agents in Man. CD Dollery & Z Bankowski, Eds. 1983.
- Monitoring and Assessment of Adverse Drug Effects. Z Bankowski & JF Dunne, Eds. 1987.
- International Reporting of Adverse Drug Reactions. Report of CIOMS Working Group I. 1990.
- International Reporting of Periodic Drug-Safety Update Summaries. Report of CIOMS Working Group II. 1993.
- Guidelines for Preparing Core Clinical-Safety Information on Drugs. Report of CIOMS Working Group III. 1994.
- Drug Surveillance: International Cooperation Past, Present and Future. Z Bankowski & JF Dunne, Eds. 1995.
- Guidelines for Preparing Core Clinical-Safety Information on Drugs (2nd edition). Report of CIOMS Working Groups III & V. 1998.
- Benefit-Risk Balance for Marketed Drugs. Evaluating Safety Signals. Report of CIOMS Working Group VI. 1999.
- Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for Their Use. 1999.
- Current Challenges in Pharmacovigilance: Pragmatic Approaches. Report of CIOMS Working Group V. 2001.
- Development and Rational Use of Standardised MedDRA Queries (SMQs) -Retrieving Adverse Drug Reactions with MedDRA. Report of the CIOMS Working Group. 2004.
- Pharmacogenetics: Towards Improving Treatment with Medicines. Report of the CIOMS Working Group. 2005.
- Management of Safety Information from Clinical Trials. Report of CIOMS Working Group VI. 2005.

- The Development Safety Update Report (DSUR): Harmonizing the Format and Content of Periodic Safety Reporting During Clinical Trials. Report of CIOMS Working Group VII. 2006.
- Practical Aspects of Signal Detection in Pharmacovigilance. Report of CIOMS Working Group VIII. 2010.

Annex 3

Data collection checklist for suspected vaccination failure

Date ____/_____/___ Case Number ----------

This checklist of criteria is derived from the definition of "vaccination failure" (see section 3.2). It is intended as a data collection template for use in study protocols and for active follow-up in clinical trials and post-licensure surveillance systems. Additional information will depend on the reason(s) for vaccination failure including the types of clinical endpoints against specific vaccines.

A. Source of information (Reported by)

	Assessing	Reporting
a. Health-care provider (indicate professional status)		
b. Other (specify)		

B. Type of vaccine for which vaccination failure is suspected

Vaccine	Strain type (specific)
Provide generic vaccine name, e.g. "influenza"	e.g. "influenza type A/H1N1"
b. Other (specify)	

C. Type of suspected vaccination failure

Type of vaccination failure (select appropriate type)	Yes	No	Unknown
a. Immunological			
If yes, give details			
b. Clinical			
If yes, describe the disease corresponding to suspected vaccination failure (name of disease, onset, how diagnosis was made etc): **For underlying disease and outcome see sections F and G**			

D. Vaccinee or subject

D 1. Demographics		
a. Patient's case ID number		
b. Date of birth	_____/_____/_____ (mm / dd / yyyy)	Unknown
c. Age when suspected vaccination failure occurred ------ years------months		Unknown
d. Sex If female, pregnancy status	M [ ] F [ ] Non-pregnant [ ] Pregnant [ ]	Unknown [ ] Unknown [ ]
e. Race/Ethnicity (if appropriate)		Unknown [ ]
f. Infants (≤12 months of age)	Gestational age ----------weeks	Unknown [ ]

D 2. Clinical / vaccination history			
a. Relevant past medical conditions that may affect the evaluation of vaccination failure? Such diseases or disorders include [list relevant conditions]: Underlying condition (disease or nutrition), specify	Yes [ ]	No [ ]	Unknown
If YES, please describe condition			
b. Vaccination history: indicate if history is: verbal [ ] or documented [ ] Unknown [ ]			

E. Details of previous vaccinations with the vaccine for which failure is suspected

E 1. Vaccine details If >1 vaccine was given				
Vaccine* previous doses (use extra sheet if > 4 doses)	Dose 1	2	3	4
a. Date of vaccination	___/___/__ [ ] Unknown	___/___/__ [ ] Unknown	___/___/__ [ ] Unknown	___/___/__ [ ] Unknown
b. Trade name				
c. Manufacturer				
d. Lot number and expiry date				
e. Diluent(s), lot number(s) and expiry date(s) [if used]				

f. Vaccine presentation	Single dose vial[] Multidose vial [ ]	Single dose vial [ ] Multidose vial [ ]	Single dose vial [ ] Multidose vial [ ]	Single dose vial [ ] Multidose vial [ ]
	Liquid [ ]		Lyophilized [ ]	Unknown
g. Vaccine reconstitution	Used within 6 hours Yes [ ] No [ ] Unknown [ ]			
If other presentation, specify----------				
h Volume (mL)				
i. Dose number				
j. If combined vaccine, specify: • antigen components ---------- • was vaccine administered at separate injection sites concomitantly? Yes[ ] No [ ]				
k. Route of administration	Oral [ ] Injection [ ] Site: Deltoid [ ] Buttock [ ] Thigh [ ] Other route of administration (specify) ---------- Unknown [ ]	Oral [ ] Injection [ ] Site: Deltoid [ ] Buttock [ ] Thigh [ ] Other route of administration (specify) ---------- Unknown [ ]	Oral[ ] Injection [ ] Site: Deltoid [ ] Buttock [ ] Thigh [ ] Other route of administration (specify) ---------- Unknown [ ]	Oral [ ] Injection [ ] Site: Deltoid [ ] Buttock [ ] Thigh [ ] Other route of administration (specify) ---------- Unknown [ ]
l. Co- administered vaccine (s): provide details a to k above (use additional sheets if necessary)	Vaccine 1	Vaccine 2	Vaccine 3	Vaccine 4
m. Person who vaccinated the subject	Nurse [ ] Other health-care provider (specify) Unknown [ ]	Nurse [ ] Other health-care provider (specify) Unknown [ ]	Nurse [ ] Other health-care provider (specify) Unknown [ ]	Nurse [ ] Other health-care provider (specify) Unknown [ ]
* Previous doses of vaccine(s) under suspicion for the same vaccine-preventable disease.				

F. Vaccination failure evaluation (performed by: give name and position)

F. 1. Usage issues	Yes	No	Insufficient evidence
a. Administration error Wrong route Suboptimal route Inadequate dose Incorrect diluent			
b. Vaccination series Incomplete Non-compliant with recommended schedule			
c. Storage-related (e.g. cold chain)			
If yes, specify --------			
d. Vaccine expired			
If yes, specify how many days/months beyond expiry ---------- (days or months)			
e. Immunization programme-related issues Suboptimal recommendations *(regarding number and time points of primary and/or booster vaccinations)* Shortage of vaccine *(leading to incomplete vaccination)*			
If yes, specify --------			
F 2. Vaccinee (Host)-related issues (laboratory confirmed)			
Immunodeficiency			
If yes, specify including lab values ----------			
Age-related maturation and senescence			
If yes, specify including lab values ----------			
Insufficient or suboptimal immune response			
If yes, specify including lab values ----------			
Interference due to other infectious agents			
If yes, specify including lab values ----------			
Waning immunity			
If yes, specify condition(s) including lab values (as appropriate)----------			
Suboptimal health status *(including underlying condition such as disease, nutrition)*			
If yes, specify including lab values ----------			

Immunological interference *(e.g. maternal antibodies, administration of immunoglobulins)*			
Pre-existing infection with pathogen targeted by the vaccine *(e.g. with specific HPV genotypes)* or vaccination during incubation period *(after exposure to pathogen)*			
If yes, specify including lab values ----------			
Immunosuppressive therapy			
If yes, specify the medication ----------			
Lack of seroconversion			
If yes, specify including lab values ----------			

G. Miscellaneous

a. What was the outcome at final follow-up?	Yes	No	Unknown
Resolved without treatment			
Resolved with treatment			
Death			
Sequelae, please specify----------			
Outcome unknown [ ]			
Any other outcome, (specify)			
b. Outcome at last follow-up			
c. Please add any other comments or a clinical narrative if you think it will add to the understanding of the suspected vaccination failure. Copy of medical record relating to the event may be attached.			

Annex 4

Workflow for revision and endorsement of Brighton Collaboration case definitions by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance

Box-1. Completed draft Brighton Collaboration documents are sent to the CIOMS/WHO WG after review by the Brighton Collaboration Reference Group and approval by the Brighton Collaboration Science Board.

Box-2. Brighton Collaboration documents are reviewed in depth by primary and secondary reviewers from the CIOMS/WHO WG, and discussed in breakout session. The recommendation for endorsement or revision from the breakout group is then made to the overall CIOMS/WHO WG, which is responsible for the decision regarding formal endorsement.

Box-3. The discussion on a given Brighton Collaboration document, including whether or not it was endorsed, is shared with the Brighton Collaboration secretariat, which coordinates the review of comments and/or edits with respective Brighton Collaboration Working Group coordinators. All comments should be discussed but the ones critical for endorsement need to have a thorough response sent back in writing to the CIOMS/WHO WG.

Box-4. For documents ***not endorsed*** by the CIOMS/WHO WG, the Brighton Collaboration secretariat sends Brighton Collaboration WG replies and the revised documents 2 weeks prior to the next CIOMS/WHO WG meeting and asks for endorsement. The overall CIOMS/WHO WG is responsible for endorsement. The Brighton Collaboration WG replies for ***endorsed*** documents are only sent for informational purposes and not for re-review.

Box-5. The revised and endorsed documents are submitted by the Brighton Collaboration for publication in *Vaccine.*

Annex 5

Suggested generic introduction for use in translation of abridged Brighton Collaboration case definitions

Introduction

The goal of the Brighton Collaboration is to facilitate the development, evaluation, and dissemination of high-quality information about the safety of human vaccines. This is achieved by developing a comprehensive set of standardized case definitions for adverse events following immunization (AEFIs) in order to promote the current understanding of immunization safety and enhance comparability of immunization safety data.

Standardized AEFI definitions are obtained by consensus of a global network of individuals and organizations concerned with immunization safety or with associated medical and methodological aspects. The entire process is outlined in the Brighton Collaboration overview paper *(1*). This will benefit vaccine scientists, health officials and health-care providers, recipients, vaccine providers, and manufacturers who need to obtain, interpret, provide, and report information on immunization safety.

The following case definition is structured in several levels of diagnostic certainty from highest to lowest.

Translation is focused on the core case definition as well as relevant sections of the preamble. General guidelines for use in post-marketing surveillance and clinical trials can be obtained in English (*2, 3*) and will be available in additional languages at a future date at https://brighton-collaboration.org/public. Please refer to the original publication for additional information (add reference as appropriate). The most up-to-date case definitions may be accessed on the Brighton Collaboration website (https://brightoncollaboration.org/public).

References:

1. Kohl KS et al. The development of standardized case definitions and guidelines for adverse events following immunization. *Vaccine*, 2007, 22:5671-5674.
2. Bonhoeffer J et al. The Brighton Collaboration Methods Working Group. Guidelines for collection, analysis and presentation of vaccine safety data in surveillance systems. *Vaccine*, 2009, 27:2289-2297.
3. Bonhoeffer J et al. The Brighton Collaboration Methods Working Group. Guidelines for collection, analysis and presentation of vaccine safety data in pre-and post-licensure clinical studies. *Vaccine*, 2009, 27:2282-2288.

Annex 6

Guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies

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Keywords: vaccine, immunization, safety, guidelines

Disclaimer: The findings, opinions and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant's organization (e.g., government, university, or corporation). Specifically, the findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Food and Drug Administration.

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1. Preamble

The following guidelines seek to standardize vaccine safety assessment by improving the accuracy and completeness of collection, analysis, and presentation of information about Adverse Events Following Immunization (AEFI) in pre-and post-licensure clinical studies (e.g., randomized controlled trials, cohort studies, case-control studies, self-controlled case series).

1.1 Need for developing guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies

Collection of accurate and complete safety data is essential in both pre- and postlicensure studies, as well as in post-licensure passive surveillance. However, the nature of safety data collected in clinical studies, comparative or non-comparative, differs from data obtained from passive surveillance monitoring.

First, the sample sizes in clinical trials are relatively small compared to the denominator for passive surveillance studies, which may be estimated in terms of AEFI reporting rates per million doses administered. In pre-licensure Phase 1 trials, the goal is to obtain preliminary data on a candidate vaccine's tolerability and safety. Sample sizes are small, often ten per group. Phase 1 trials can begin to document common, chiefly mild and transient AEFI. Sample sizes are larger in Phase II (expanded dose ranging) studies in which the goal is to estimate the dose/response curve and to choose the optimal dose for the target population at risk. Usually, 100 to 300 individuals per group may be included. This sample size permits broader safety data collection, and a better understanding of the nature of the safety/tolerability profile suggested in Phase I. In Phase III, the primary goal is typically to establish proof of efficacy. Sample sizes typically range between 500 and 4000, but may be as high as 30,000 per group (e.g., vaccinees vs. placebo recipients). These sample sizes and the use of double-blinded, randomized, controlled trial designs, permit excellent definition of a vaccine's safety/tolerability profile for commoner AEFI, and assessment of the vaccine-attributable risk of these events. Rates of less common AEFI may also be evident, but rates of rare AEFI (those with rates of occurrence of less than 1 per 100,000 vaccinees or placebo recipients) require post-licensure surveillance data.

Second, particularly in early phase trials, even a single serious AEFI can lead to a comprehensive review to assess whether the AEFI was caus-

ally related to the experimental vaccine or not. Pending outcome of the review, the trial may be halted. Detection of an AEFI occurring at a rate high enough to be detectable in such small groups could lead to the abandonment of the candidate vaccine.

Thus, the level of detail, accuracy and completeness of AEFI reports is a vital factor in the generation of reliable data on vaccine product safety. This is particularly important in Phase I-III clinical trials, because safety information will be included in package circulars and, in rare cases, may lead to product withdrawal when the causal relationship between a given vaccine and a serious AEFI is proven and the frequency is perceived as generating an unfavorable risk to benefit ratio.

However, because of the heterogeneity of case definitions and methods for data collection, analysis and presentation of AEFI, valuable information is often not available and data from different studies are challenging to compare [1,2]. The guidelines proposed in this paper aim to address this need for improved data comparability. Standardized collection of complete information on AEFI will facilitate data comparability between vaccine safety studies. This will improve the scientific understanding of AEFI and add to the value of data derived from pre- and post-licensure clinical studies.

1.2 Methods for the development of the proposed guidelines

Following the standard process [1], a Brighton Collaboration *Methods* Working Group was formed in July 2002 with 17 members from clinical, public health, manufacturing and professional organizations and began to develop these guidelines. The member composition and results of the web-based surveys completed by the reference group and subsequent discussions in the working group can be viewed at: https://brightoncollaboration.org/public.

The primary aim of the working group was to develop a methodological framework for the development of standardized case definitions of AEFI and guidelines for the collection, analysis and presentation of vaccine safety data in Brighton Collaboration working groups. To guide decision-making, we searched textbooks, bibliographic databases, reference lists, and personal files for relevant information, including existing recommendations, and articles describing relevant methodological research. During two years of consensus formation in regular conference calls and email exchange, the group identified a core set of essential guidelines for the

collection, analysis and presentation of AEFI data. In a web-based survey of the draft document comments of additional vaccine safety professionals were invited. The revised document was circulated among Brighton Collaboration working group coordinators for consideration and implementation in the guideline section of their respective documents. The guidelines were finalized upon review by the WHO/CIOMS Working Group on Vaccine Pharmacovigilance. Similar to all Brighton Collaboration case definitions and guidelines, review and, when indicated, revision of the guidelines is planned on a regular basis (i.e., every 3–5 years), or more often, when needed.

1.3 Use of the proposed guidelines

It was the consensus of the *Methods* Working Group to recommend the following guidelines as a desirable standard for collection, analysis and presentation of vaccine safety data. These guidelines are intended to be applicable in diverse geographic, administrative, and cultural regions, regardless of differences in the availability of health care resources. However, the group recognizes that implementation of all guidelines might not be possible in all settings. The availability of information may vary depending upon resources, the geographical region, and the study design. Also, as explained in more detail previously [1], these guidelines have been developed for guidance only, and are not considered a mandatory requirement for data collection, analysis, or presentation. Additional data may be collected, analyzed, and presented as deemed necessary by the investigators. Protocols for clinical trials and other comparative studies should be designed to optimize safety reporting, and to facilitate data collection and analysis according to the guidelines presented in this document.

The proposed guidelines are also relevant for assessment of adverse events following future vaccines, including those targeting chronic diseases, (e.g., diabetes mellitus, rheumatoid arthritis), therapeutic vaccines (e.g., tumor vaccines), as well as DNA vaccines, mucosal vaccines, or vaccines with slow-release delivery systems. The proposed guidelines are not intended to guide or establish criteria for management of ill infants, children, or adults. They are also not regulatory in nature, and are not intended to replace established or mandated processes of reporting.

The proposed guidelines are harmonized with the pertinent guidelines by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guide-

lines as well as the form for reporting of drug adverse events developed by the Council for International Organizations of Medical Sciences (CIOMS) [3,4]. However, the expected minimum set of information to be collected exceeds the minimum set proposed by ICH/CIOMS.

Complementary to these general guidelines for pre- and post-licensure clinical studies, the Brighton Collaboration has also developed guidelines for collection, analysis and presentation of vaccine safety data in surveillance systems [5]. Both guidelines are reflected in the specific guidelines accompanying every Brighton Collaboration case definition for specific AEFI [6]. While investigators are encouraged to primarily refer to the specific case definitions and guidelines, these general guidelines represent an overall framework for collection, analysis and presentation of vaccine safety data, in particular for those AEFI for which no specific guidelines are available and for those studies collecting data on a number of different AEFI.

The working group recognizes and emphasizes that AEFI may be temporally associated with, but not necessarily caused by administration of a vaccine. The following guidelines outline requirements for high-quality information on reported AEFI, without regard to whether there is a causal relationship to a prior immunization. Causality assessment of individual case reports or based on data from epidemiologic studies are separate steps of analysis, which may be done subsequently [7,8].

1.4 Purpose of appended reporting form

The purpose of the appended reporting form is to outline the data fields needed to solicit complete information on AEFI consistent with Brighton Collaboration data collection guidelines for clinical studies. It is intended as a data collection template for use in study protocols and active follow-up in surveillance systems. Additional information or a different format depending on the study question and setting may be required.

2. Guidelines

2.1. Data collection

The following guidelines represent a desirable standard for collection of vaccine safety data. In accordance with general drug safety guidelines by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as well as

the form for reporting of drug adverse events developed by the Council for International Organizations of Medical Sciences (CIOMS), data elements to be collected for the assessment of an AEFI are: an identifiable reporter and patient, one or more prior immunizations, and a detailed description of the AEFI [3,4]. The Brighton Collaboration's *Methods* Working Group developed guidelines 2, 5, 6, 11, 12, and 17-26 below to address these international requirements. Since the information on an AEFI may initially be incomplete, efforts should be made to gather more comprehensive information. The additional guidelines have been developed as guidance for the collection of additional information to allow for a more comprehensive understanding of a given AEFI. Appendix 1 provides an example of how these guidelines could be applied in a data collection form for primary reports and/or follow-up.

2.1.1. Source of information/ reporter

For all cases and/or all study participants, as appropriate, the following information should be recorded:

1) Date of report.

2) Name and contact information of person reporting[a] and/or assessing or diagnosing the AEFI in accordance with country-specific data protection law.

3) Relationship to the patient (e.g., immunizer [clinician, nurse], family member [indicate relationship], other).

4) Name and contact information of the investigator responsible for the subject in accordance with the data protection law.

2.1.2. Vaccinee/control

For all cases and/or all study participants, as appropriate, the following information should be recorded:

2.1.2.1. Demographics

5) Case/study participant identifiers (first name initial followed by last name initial), or code, or as otherwise specified in country-specific data protection laws

6) Date of birth, age, sex, ethnicity (if appropriate).

7) For infants (≤12 months of age): Gestational age and birth weight, if applicable.

2.1.2.2. Clinical and immunization history

8) Medical history including hospitalizations, underlying diseases/disorders, pre-immunization signs and symptoms that may affect the evaluation of an AEFI.

9) Any medication history prior to, during, and after vaccination including prescription and non-prescription medication (e.g., herbal or homeopathic medication) as well as medication with long half-life or long-term effect (e.g., immunoglobulins, blood transfusions, immunosuppressants) that could affect the evaluation of an AEFI, but other than treatment given for the AEFI.

10) Immunization history, i.e. previous immunizations and any AEFI including recurrence of similar AEFI and their number in series, if available.

2.1.3. Details of the immunization

For all cases and/or all study participants, as appropriate, the following information should be recorded:

11) Date and time of immunization.

12) Description of vaccine(s): name of vaccine, manufacturer, lot number, multi- or mono-dose vial, pre-filled syringe, volume (e.g., 0.25 ml, 0.5 ml, etc.), number of dose (e.g. first, second or third), if part of a series of immunizations against the same disease (s), lot of diluent, and expiration date.

13) Anatomical sites (including left or right side) of all immunizations (e.g., vaccine A in proximal left lateral thigh, vaccine B in left deltoid).

14) Method of administration (e.g., intramuscular, intradermal, subcutanous, oral, intranasal, needle-free (including type and size) or other injection devices.

15) Needle length and gauge.

2.1.4. The adverse event

For all cases and/or all study participants, as appropriate, the following information should be recorded:

16) Criteria fulfilled to meet a case definition and other signs or symptoms indicative of an AEFI.

17) Detailed clinical description of the event including the quality of symptoms (e.g., type of pain).

18) Date and time of: onset[b], first observation[c], diagnosis[d], end of an episode[e], and final outcome[f].

19) Concurrent signs, symptoms, and diseases other than the event described.

20) Recurrence of event after initial AEFI onset or occurrence of similar event prior to immunization.

21) Values and units of routinely measured parameters (cm, °C, etc.) – in particular those indicating the severity of the event.

22) Method of measurement (e.g., type of thermometer, oral or other specific route, duration of measurement, etc.).

23) Results of laboratory examinations, surgical and/or pathological findings and diagnoses.

24) Treatment given for the AEFI (i.e., systemic and/or local site treatment).

25) Outcome[f] at last observation of each AEFI should be clearly described (e.g., recovery to pre-immunization health status, spontaneous resolution, therapeutic intervention, persistence of the event, sequelae, death, or description of any other outcome).

26) Medical review of the event (i.e., patient seen by physician), if applicable.

27) Presence or absence of concurrent local disease outbreaks, as appropriate.

28) Further doses given and the outcome (i.e. re-vaccination).

2.1.5. Miscellaneous/ general recommendations

29) The duration of surveillance for AEFI should be predefined and depends on

- biologic characteristics of the vaccine e.g., live attenuated versus inactivated component vaccines;
- composition of the vaccine (e.g. adjuvants);
- biologic characteristics of the vaccine-targeted disease;
- biologic characteristics of the AEFI including patterns identified in previous studies (e.g., early-phase trials); and

- biologic characteristics of the vaccine recipient (e.g., nutrition, underlying disease like immunodepressing illness).

30) The methods of data collection should be consistent within and between study groups, if applicable.

31) Reports of AEFI should be collected regardless of the time elapsed between vaccination and the adverse event. If this is not feasible due to the study design, the study periods during which safety data are being collected should be clearly defined.

32) Criteria defining pre-specified AEFI should be solicited at a predefined frequency.

33) The duration of follow-up for AEFI, reported during the surveillance period, should be predefined.

34) Follow-up of reported events should attempt to verify and complete the collection of information as outlined in section 2.1. In particular, for all cases at any level of diagnostic certainty and for reported events with insufficient evidence (see section 2.2.), all signs and symptoms indicative of the respective AEFI should be recorded.

35) Investigators should provide guidance to reporters to optimize the quality and completeness of information provided.

2.2. Data analysis

The following guidelines represent a desirable standard for analysis of data on an AEFI to allow for comparability of data. Additional data collected may be analyzed depending on the study question and setting.

36) Reported events could be classified in one of the following categories. Events that meet the case definition should be classified according to the levels of diagnostic certainty as specified in the case definition – Brighton Collaboration if available, or other [6]. Events that do not meet the case definition at any of the levels of diagnostic certainty to make the diagnosis of a given AEFI, could be classified in the additional categories for analysis.

2.2.1. Event classification[g]

Event meets case definition (Main categories)

1. Level 1 of diagnostic certainty

2. Level 2 of diagnostic certainty

3. Level 3 of diagnostic certainty

Event does not meet case definition (Additional categories for data analysis)

4. Reported *[AEFI]* with insufficient evidence to meet the case definition[h]

5. Not a case of *[AEFI]*[i]

37) The interval between immunization and an AEFI should be specified by using the date/time of immunization and either the date/time of onset[b] or first observation[c] or diagnosis[d], whichever is most appropriate for the AEFI. Whatever dates are used, they should be used consistently within and across study groups.

38) The duration of an AEFI, if applicable, should be analyzed as the interval between date/time of onset[b] or first observation[c] or diagnosis[d] and the end of episode[e] or final outcome[f]. Whatever start and ending dates are used, they should be used consistently within and across study groups.

39) If a given AEFI occurs intermittently, the event corresponding to the greatest magnitude of adverse event should be used as the basis for categorization. Also the frequency and pattern of re-occurrence (e.g., periodicity) should be analyzed.

40) If more than one measurement of a particular parameter is taken and recorded, the value corresponding to the greatest magnitude of the adverse event should be used as the basis for categorization (e.g., highest body temperature). Analysis may also include other characteristics like qualitative patterns of criteria defining the event (e.g., periodicity, frequency, fever-days, etc).

41) The distribution of data (as numerator and denominator data) should be analyzed in predefined increments (e.g., measured values, times), where applicable. When the number of cases reported is too small for stratification, the respective values or time course should be described for each case.

42) AEFI should be analyzed by study arm and dose.

43) Results obtained in subjects receiving a vaccine under study ideally should be compared with those obtained from appropriately selected and documented control groups.

2.3. Data presentation

The following guidelines represent a desirable standard for presentation or publication of analyzed AEFI data to allow comparability in vaccine safety. They are not guidelines for primary reporting of AEFI to a study monitor. Additional information collected and analyzed may be presented depending on the study question and setting. It is recommended to also refer to existing guidelines including CONSORT (Consolidated standards of reporting trials), QUORUM (Improving the quality of reports of meta-analyses of randomized controlled trials), TREND (Transparent reporting of evaluations with non-randomized designs), STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and MOOSE (Meta-analysis of observational studies in epidemiology) for presentation and publication of randomized controlled trials, meta-analyses, non-randomized designs, observational studies, and systematic reviews of vaccine safety studies, respectively [9-13].

44) AEFI data should be presented in accordance with the data analysis guidelines in section 2.2.

45) Terms to describe an AEFI such as “low-grade”, “mild”, “moderate”, “high”, “severe” or “significant” are highly subjective, prone to wide interpretation, and should be avoided unless validated or clearly defined.

46) Data should be presented with numerator and denominator (and not only in percentages or graphical illustrations) and by lot or vaccine, if applicable.

47) If the median and range are the appropriate statistical descriptors, and the distribution of data is skewed, then the mean and standard deviation should also be provided to permit meta-analysis.

48) The incidence[j] of events meeting the case definition should be presented and clearly identified as such in the text.

49) Any publication of AEFI data should include as detailed as possible a description of the methods used for data collection and analysis. It is essential to specify

- the study design;
- the study group(s) including comparison group(s);
- the instrument of data collection (e.g., standardized questionnaire, diary card);

- the method, frequency, and duration of monitoring for AEFI;
- whether the day of immunization was considered "day one" or "day zero" in the analysis;
- whether the date of onset[b] and/or the date of first observation[c] and/or the date of diagnosis[d], and the end of episode[e] and/or final outcome[f] were used for analysis;
- the data analysis plan per protocol, and the statistical plan; and any amendments to these sections of the protocol added during the study;
- the trial profile, indicating participant flow during a study including drop-outs and withdrawals to indicate the size and nature of the respective groups under investigation; and
- Reference of the case definition used (Brighton Collaboration or other) for AEFI in the abstract or methods section of a publication[k].

Notes for guidelines

---

[a] If the reporting center is different from the vaccinating center, appropriate and timely communication of the adverse event should occur.

[b] The date and/or time of onset is defined as the time post immunization, when the first sign or symptom indicative of the AEFI occurred. This may only be possible to determine in retrospect.

[c] The date and/or time of first observation of the first sign or symptom indicative of the AEFI can be used, if date/time of onset is not known.

[d] The date of diagnosis of an episode is the day post immunization the event met the case definition at any level.

[e] The end of an episode is defined as the time the event no longer meets the case definition.

[f] An AEFI not resolved at the end of a predefined follow-up period may be followed-up as clinically necessary, and additional reporting should be encouraged in order to describe progress until the final outcome. "Persistence of event" refers to events continuing to meet the case definition beyond the follow-up period. "Sequelae" are long term clinical consequences resulting from the event.

[g] If the lowest level of a case definition is not met, it should be ruled out that any of the higher levels of diagnostic certainty are met and the event should be classified in category 4 or 5.

[h] If the evidence available for an event is insufficient to permit classification by any level of diagnostic certainty (e.g. because of missing information), such an event should be categorized as "reported [*AEFI*] with insufficient evidence to meet a case definition". Notations should be made as to what evidence is missing.

[i] If there is adequate evidence that an event does not meet a case definition, such an event should be rejected and should be reported as "Not a case of [AEFI]". Such evidence is considered adequate, if an exclusion criterion is met, or investigation reveals a negative finding of a necessary criterion (necessary condition) for diagnosis. Such an event should be rejected and classified as "Not a case of *[AEFI]"*

[j] e.g., cumulative incidence rate: 10 cases of a given AEFI among 1 million doses administered; or incidence rates: 3 cases of a given AEFI on day 1, 2 cases on day 2, 10 cases on day 3 following immunization, or 0 cases after the first dose, 1 case after the second dose, 10 cases after the third dose.

[k] Use of this or AEFI specific documents developed by the Brighton Collaboration should be referenced by referring to the link on the Brighton Collaboration website (https://brightoncollaboration.org/public).

Acknowledgements

The authors are grateful for the support and helpful comments from members of the Brighton Collaboration Steering Committee during the time of the development of this document, who are not already included as authors (Elisabeth Loupi, Miles Braun, Brigitte Keller Stanislawski), and participants in the Reference Group (Raymundo Azevedo, Rolando Ochoa Azze, Michael Blum, Dean Blumberg, Thomas Cherian, Bakary Drammeh, Philippe Duclos, Delia A. Enria, Birgitta Evengard, Farhad Handjani, John Hansen, Marcy Connell Jones, Daniele Kohl, Jerry Labadie, Glenda Lawrence, David G. McIntosh, Suzanne Menard, Tony Nelson, Suchitra Nimmannitya, James Oleske, Gabriele Poerschke, Keith Powell, Edward Rothstein, Synne Sandbu, Ines Schoendorf, Françoise Sillan, Russell Steele, Gillian A. Stoltman, Amina Tebaa, Eveline Toth, Alberto Tozzi, John Treanor, Patricia Vermeer, Beverly Warden), and for the harmonization work by Jane Gidudu and Michael Büttcher.

Finally, we would like to thank the members of the WHO/CIOMS Working Group on Vaccine Pharmacovigilance (http://www.cioms.ch/activities/frame_vaccpharma.htm) for the review of, constructive comments on, and endorsement of this document.

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Sample Report Form for Adverse Events Following Immunization (for clinical studies)

ADVERSE EVENT REPORT

Patient and reporter identity is confidential. Complete the form to the best of your abilities.

Required fields are marked with an asterisk (*) and printed in bold. Please indicate units used (for fever, for length, for lab test results, etc.).

Should you require more space than provided to report all relevant data, please use additional pages and refer to the respective questions on the form.

A. Source of Information/ Reporter

Study number: _____
Subjectnumber: _____
Case no.: _____

1) Date of this report*: ___/___/___ (DD/MM/YYYY) **2) Report type*:** ☐Initial ☐Follow-up

3) First name*: _____ Middle initial: _____ **Last name*:** _____

4) Phone: +____ (_____)_____Fax: +____ (_____)_____

5) Address*: _____ **Street*:** _____

Country*: _____ State: _____ **Postcode/ ZIP*:** _____**City*:** _____ email:_____

6) Relation to patient: ☐Investigator ☐Patient/ Family member (indicate relationship) ☐Manufacturer ☐Other(specify)_____

B. Vaccinee/Control

7) Patient initials[1] (first name/ last name) ___ /____

8) Birth date*: ___/___/___ (DD/MM/YYYY) **9) Sex*:** ☐M ☐F ☐Unknown **10) Infants:** Gestational age:_____ birth weight:_____

11) Was the patient seen by a physician for the adverse event reported on this form? ☐Yes ☐No ☐Unknown

12) Pre-vaccination signs or symptoms on day of vaccination (e.g. cold, fever): ☐Yes ☐No ☐Unknown If YES, please describe:

_____

_____

13) Any medication prior to, during, and after the adverse event including prescription and non-prescription medication (e.g., herbal or homeopathic medication) as well as medication with long half-life or long-term effect (e.g., immunoglobulins, blood transfusion, immunosuppressants, oral or intravenous corticosteroids), that could affect the evaluation of an AEFI, but other than treatment given for the AEFI. ☐Yes ☐No ☐Unknown
If YES, please specify:

_____

_____

14) Medical history: List any prior hospitalizations and diagnoses, or other significant medical history of any medical or psychological disorders or serious injuries including treatment (e.g., pregnant, allergies, seizures, events similar to or related to the AEFI)

_____

_____

15) Did the patient experience any adverse events other than the current one to previous doses of the same vaccine? ☐Yes ☐No ☐Unknown
If YES, describe in detail including dates of occurrence:

_____

_____

16) Relevant family history? ☐Yes ☐No ☐Unknown If yes, please specify:

_____

_____

[1] While the name or initials of the patient would be highly valuable for follow-up, it is recognized that this information is often subject to the provisions of the respective national regulatory agency's privacy act or the country-specific data protection law.

C. Details of Immunization

17) Please provide available details of the patient's vaccination history.*

Date (DD/MM/YYYY)	Time (hh:mm)	Vaccine	Manufacturer	Lot number	Lot of diluent	Multi-dose package[1]	Expir. date (DD/MM/YYYY)	Dose[2]	No. of dose in series[3]	Route[4]	Anatomical site[5]	Device[6]	Source of information[7]

[1] e.g., 50 ml vial; [2] e.g., 1 ml; [3] against same disease; [4] route of administration (e.g., i.m., s.c.); [5] e.g. left arm, deltoid area; [6] e.g., syringe; needle: 4 cm, 18"; [7] e.g., medical record, history.

D. The Adverse Event

18) Final diagnosis of AE: _____ 19) Date and time of diagnosis: ___/___/___ (DD/MM/YYYY)

20) Date and time of onset (time of first sign or symptom indicative for the primary AEFI)*: ___/___/___ (DD/MM/YYYY)

21) Describe the sequence of events including times, dates, symptoms, signs and test results supporting diagnosis*:

_____
_____
_____
_____
_____
_____

22) List any treatments given for the AEFI including times and dates:

_____
_____

23) Has patient's condition returned to pre-vaccination health status? ☐Yes ☐No ☐Unknown

If YES, indicate when pre-vaccination heath status was reached: ___/___/___ (DD/MM/YYYY)

If NO, indicate whether the patient has any persistent signs or symptoms, residual disability or sequelae, and what has happened to date:

_____
_____
_____

24) Was the patient re-vaccinated (i.e., were further doses applied?) ☐Yes ☐No ☐Unknown

If YES, describe the outcome

_____
_____

Annex 7

Guidelines for collection, analysis and presentation of vaccine safety data in surveillance systems

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Keywords: vaccine, immunization, safety, guidelines

Disclaimer: The findings, opinions and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant's organization (e.g., government, university, or corporation). Specifically, the findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Food and Drug Administration.

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1. Preamble

The following guidelines seek to standardize vaccine safety assessment by improving the accuracy and completeness of collection, analysis, and presentation of information about adverse events following immunization (AEFI) as reported to safety surveillance systems.

1. Need for developing guidelines for collection, analysis and presentation of vaccine safety data in surveillance systems

Accurate and timely documentation of safety data is essential to maintain public confidence in vaccine safety and in immunization programs. This in turn is pivotal for maintaining the high vaccination coverage rates needed for effective disease control and prevention.

Passive surveillance of adverse events following immunization (AEFI) is important, because documentation of the safety profile of each vaccine depends on timely, accurate and complete reporting of such AEFI, whether or not the observer considers if the AEFI was caused by a vaccine. Common, generally mild AEFI typically are first detected in pre-licensure clinical trials and are usually listed in package circulars (product labels) of marketed vaccines. If pre-licensure trials reveal any serious AEFI causally related to vaccination and occurring at sufficient frequency to generate an unfavorable risk to benefit ratio, such a vaccine is usually not licensed. Rare, serious AEFI with marketed vaccines generally occur at rates too low to detect in the size of populations included in pre-licensure clinical trials.

The level of detail, accuracy and completeness of such AEFI reports is a vital factor in the post-licensure generation of data on vaccine product safety. Reviews of AEFI report patterns generate signals, such as clusters or unusual frequencies of reports, triggering studies, specifically designed to assess whether a vaccine is the cause of an AEFI or not. Periodic reviews may lead to changes in recommendations and safety information in package circulars and, in rare cases, to product withdrawal when the causal relationship between a given vaccine and a serious AEFI is proven and the AEFI frequency is judged to have an unfavorable risk to benefit ratio.

Passive surveillance reporting has inherent limitations and difficulties, including underreporting, variable and often incomplete reports, high frequency of incomplete follow-up or outcome information, limited or no access to hospital or laboratory records, and a lack of a reliable denominator. Passive surveillance cannot determine whether the relationship between

an AEFI and a vaccine is causal or merely temporal. These deficiencies in quality, however, are partly balanced by the large numbers of reports received over time, which permit epidemiologic monitoring, analysis and assessment of trends in reporting.

However, because of the heterogeneity of case definitions and methods for data collection, analysis and presentation of AEFI, valuable information is often not available and data from different surveillance systems are challenging to compare [1,2]. The guidelines proposed in this paper aims to address the need for improved data comparability. Standardized collection of complete information on AEFI will facilitate data comparability between surveillance systems and potentially with data from clinical trials. This will improve the scientific understanding of AEFI and add to the value of data derived from the individual surveillance systems.

1.2 Methods for the development of the proposed guidelines

Following the standard process [1], a Brighton Collaboration *Methods* Working Group was formed in July 2002 with 17 members from clinical, public health, manufacturing and professional organizations and began to develop these guidelines. The member composition and results of the web-based surveys completed by the reference group and subsequent discussions in the working group can be viewed at: https://brightoncollaboration.org/public.

The primary aim of the working group was to develop a methodological framework for the development of standardized case definitions of AEFI and guidelines for the collection, analysis and presentation of vaccine safety data in Brighton Collaboration working groups. To guide decision-making, we searched textbooks, bibliographic databases, reference lists, and personal files for relevant information, including existing recommendations, and articles describing relevant methodological research. During two years of consensus formation in regular conference calls and email exchange, the group identified a core set of essential guidelines for the collection, analysis and presentation of AEFI data. In a web-based survey of the draft document, comments of additional vaccine safety professionals were invited. The revised document was circulated among Brighton Collaboration working group coordinators for consideration and implementation in the guideline section of their respective documents. The guidelines were finalized upon review by the WHO/CIOMS Working Group on Vaccine Pharmacovigilance. Similar to all Brighton Collaboration case defini-

tions and guidelines, review and, when indicated, revision of the guidelines is planned on a regular basis (i.e., every 3–5 years), or more often, when needed.

1.3 Use of the proposed guidelines

It was the consensus of the Methods Working Group to recommend the following guidelines as a desirable standard for collection, analysis, and presentation of vaccine safety data. These guidelines are intended to be applicable in diverse geographic, administrative, and cultural regions, regardless of differences in the availability of health care resources. However, the group recognizes that implementation of all guidelines might not be possible in all settings. The availability of information may vary, depending upon available resources, the geographical region, the professional background of the reporter, and the degree to which reporting is stimulated, promoted or otherwise facilitated. Also, as explained in more detail previously [1], these guidelines have been developed for guidance only, and are not considered a mandatory requirement for data collection, analysis, or presentation. Additional data may be collected, analyzed, and presented as deemed necessary by the investigators.

The proposed guidelines are also relevant for assessment of adverse events following future vaccines, including those targeting chronic diseases, (e.g. diabetes mellitus, rheumatoid arthritis), therapeutic vaccines (e.g. tumor vaccines), as well as DNA vaccines, mucosal vaccines, or vaccines with slow-release delivery systems. The Guidelines are not intended to guide or establish criteria for management of ill infants, children, or adults. They are also not regulatory in nature, and are not intended to replace established or mandated processes of reporting.

The proposed guidelines are harmonized with the pertinent International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines as well as the Council for International Organizations of Medical Sciences (CIOMS) form for reporting of drug adverse events [3,4]. However, the expected minimum set of information to be collected exceeds the minimum set proposed by ICH/CIOMS.

Complementary to these general guidelines for surveillance systems, the Brighton Collaboration has also developed general guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical trials [5]. They are also reflected in the specific guidelines

accompanying every Brighton Collaboration case definition for specific AEFI [6]. While investigators are encouraged to primarily refer to the specific case definitions and guidelines, these general guidelines represent an overall framework for collection, analysis and presentation of vaccine safety data, in particular for those AEFI for which no specific guidelines are available and for those studies collecting data on a number of different AEFI.

The working group recognizes and emphasizes that AEFI may be temporally associated with, but not necessarily caused by, administration of a vaccine. The following guidelines outline requirements for high-quality information on reported AEFI, without regard to whether they are causally related to a prior immunization. Causality assessment for individual case reports or based on data from epidemiologic studies are separate steps of analysis, which may be done subsequently [7,8].

1.4. Purpose of appended reporting form

The purpose of the attached reporting form is to outline the data fields needed to solicit complete information on AEFI consistent with Brighton Collaboration data collection guidelines for surveillance systems. It is intended as a data collection template for use in study protocols and active follow-up in surveillance systems. Additional information or a different format depending on the study question and setting may be required.

2. Guidelines

2.1 Data collection

The following guidelines represent a desirable standard for collection of vaccine safety data. In accordance with general drug safety guidelines by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as well as the form for reporting of drug adverse events developed by the Council for International Organizations of Medical Sciences (CIOMS), data elements to be collected for the assessment of an AEFI are: an identifiable reporter and patient, one or more prior immunizations, and a detailed description of the AEFI [3,4]. The Brighton Collaboration's *Methods* Working Group developed guidelines 2, 4, 5, 10, 11, 17-27 to address these international requirements. Since the information on an AEFI may initially be incomplete, efforts should be made to gather more comprehensive information. The

additional guidelines have been developed as guidance for the collection of additional information to allow for a more comprehensive understanding of a given AEFI. Appendix A provides an example of how these guidelines could be applied in a data collection form for primary reports and/or follow-up.

2.1.1. Source of information/ reporter

For all cases and/or all study participants, as appropriate, the following information should be recorded:

1) Date of report.

2) Name and contact information of person reporting[a] and/or assessing or diagnosing, the AEFI, in accordance with country-specific data protection law.

3) Relationship to the patient (e.g., immunizer [clinician, nurse], family member [indicate relationship], other).

2.1.2. Vaccinee

For all cases and/or all study participants, as appropriate, the following information should be recorded:

2.1.2.1. Demographics

4) Case/study participant identifiers (first name initial followed by last name initial), or code, or as otherwise specified in country-specific data protection law.

5) Date of birth, age, sex, ethnicity (if appropriate).

6) For infants (<12 months of age): Gestational age and birth weight, if applicable.

2.1.2.2. Clinical and immunization history

7) Medical history including hospitalizations, underlying diseases/disorders, pre-immunization signs and symptoms, that may affect the evaluation of an AEFI.

8) Any medication history prior to, during, and after vaccination including prescription and non-prescription medication (e.g., herbal or homeopathic medication) as well as medication with long half- life or long term effect (e.g., immunoglobulins, blood transfusions, immu-

nosuppressants) that could affect the evaluation of an AEFI, but other than treatment given for the AEFI.

9) Immunization history, i.e. previous immunizations and AEFI, including recurrence of similar AEFI and their number in series, if available.

2.1.3. Details of the immunization

For all cases and/or all study participants, as appropriate, the following information should be recorded:

10) Date and time of immunization.

11) Description of vaccine(s): Name of vaccine, lot number.

12) Additional description of vaccine(s): Manufacturer, dose, multi- or mono-dose, pre-filled syringe, volume (e.g., 0.25 ml, 0.5 ml, etc) and number of dose (e.g. first, second or third), if part of a series of immunizations against the same disease, lot of diluent, and expiration date.

13) Anatomical sites (including left or right side) of all immunizations (e.g., vaccine A in proximal left lateral thigh, vaccine B in left deltoid).

14) Method and route of administration (e.g., intramuscular, intradermal, subcutanous, oral, intranasal, needle-free (including type and size) or other injection devices.

15) Needle length and gauge.

2.1.4. The adverse event

For all cases and/or all study participants, as appropriate, the following information should be recorded:

16) Criteria fulfilled to meet of a case definition and other signs or symptoms indicative of an AEFI.

17) Detailed clinical description of the event including the quality of symptoms (e.g. type of pain).

18) Date and time of: onset[b], first observation[c], diagnosis[d].

19) Date and time of (additional details): end of an episode[e], and final outcome[f].

20) Concurrent signs, symptoms, and diseases other than the event described.

21) Recurrence of event after initial AEFI onset or occurrence of similar event prior to immunization.

22) Values and units of routinely measured parameters (cm, °C, etc.) – in particular those indicating the severity of the event.

23) Method of measurement (e.g., type of thermometer, oral or other specific route, duration of measurement, etc.).

24) Results of laboratory examinations, surgical and/or pathological findings and diagnoses.

25) Treatment given for the AEFI (i.e., systemic and/or local site treatment).

26) Outcome[f] at last observation of each AEFI should be clearly described (e.g., recovery to pre-immunization health status, spontaneous resolution, therapeutic intervention, persistence of the event, sequelae, death, or description of any other outcome).

27) Medical review of the event (i.e., patient seen by physician), if applicable.

28) Presence or absence of concurrent local disease outbreaks, as appropriate.

29) Further doses given and the outcome (i.e. re-vaccination).

2.1.5. Miscellaneous/ general recommendations

30) The duration of surveillance for AEFI should be predefined based on

- biologic characteristics of the vaccine e.g., live attenuated versus inactivated component vaccines;
- composition of the vaccine (e.g., adjuvants);
- biologic characteristics of the vaccine-targeted disease;
- biologic characteristics of the AEFI including patterns identified in previous studies and/or surveillance; and
- biologic characteristics of the vaccine recipient (e.g., nutrition, underlying disease like immunodepressing illness).

31) Reports of AEFI should be collected regardless of the time elapsed between vaccination and the adverse event.

32) Follow-up of reported events should attempt to verify and complete the collection of information as outlined in section 2.1. In particular,

for all cases at any level of diagnostic certainty and for reported events with insufficient evidence (see section 2.2.), all signs and symptoms indicative of the respective AEFI should be recorded.

33) Surveillance systems should provide guidance to reporters to optimize the quality and completeness of information provided. This might be done on the (electronic) form itself, or through readily available promotional materials of the surveillance system.

2.2. Data analysis

The following guidelines represent a desirable standard for analysis of data on an AEFI to allow for comparability of data. Additional data collected may be analyzed depending on the study question and setting.

34) Reported events could be classified in one of the following categories. Events that meet the case definition should be classified according to the levels of diagnostic certainty as specified in the case definition – Brighton Collaboration if available, or other [6]. Events that do not meet the case definition at any of the levels of diagnostic certainty to make the diagnosis of a given AEFI, could be classified in the additional categories for analysis.

2.2.1. Event classification[g]

Event meets case definition (Main categories)

1. Level 1 of diagnostic certainty
2. Level 2 of diagnostic certainty
3. Level 3 of diagnostic certainty

Event does not meet case definition (Additional categories for analysis)

4. Reported *[AEFI]* with insufficient evidence to meet the case definition[h]
5. Not a case of *[AEFI]*[i]

35) The interval between immunization and an AEFI should be specified by using the date/time of immunization and either the date/time of onset[b] or first observation[c] or diagnosis[d], whichever is most appropriate for the AEFI.

36) The duration of an AEFI, if applicable, should be analyzed, wherever possible in surveillance systems, as the interval between date/time of

onset[b] or first observation[c] or diagnosis[d] and the end of episode[e] or final outcome[f].

37) If a given AEFI occurs intermittently, the event corresponding to the greatest magnitude of adverse experience should be used as the basis for categorization. Also the frequency and pattern of re-occurrence (e.g. periodicity) should be analyzed.

38) If more than one measurement of a particular parameter is taken and recorded, the value corresponding to the greatest magnitude of the adverse event should be used as the basis for categorization (e.g., highest body temperature). Analysis may also include other characteristics like qualitative patterns of criteria defining the event (e.g., periodicity, frequency, fever-days, etc).

39) The distribution of data (e.g., measured values, times) should be analyzed as numerator and denominator data and by lot, by vaccine and in predefined increments, where applicable. When the number of cases reported is too small for stratification, the respective values or time course should be described for each case.

2.3 Data presentation

The following guidelines represent a desirable standard for presentation or publication of analyzed AEFI data to allow comparability of vaccine safety data. They are not guidelines for primary reporting of AEFI to a surveillance system. Additional information collected and analyzed may be presented depending on the study question and setting.

40) AEFI data should be presented in accordance with the data analysis guidelines in section 2.2.

41) Terms to describe an AEFI such as “low-grade”, “mild”, “moderate”, “high”, “severe” or “significant” are highly subjective, prone to wide interpretation, and should be avoided unless validated or clearly defined.

42) Data should be presented with numerator and denominator (and not only in percentages or graphical illustrations) and by lot or vaccine, where applicable. The exact number of doses administered is generally not available as a denominator for analysis of passive surveillance data. The source of approximate denominators (e.g., population-based coverage data derived from Ministry of Health; doses sold by manufacturer/distributer) and the method of calculating such denominators

(e.g., total doses administered (= doses distributed minus 10% percent of storage and wastage), should be presented.

43) If the median and range are the appropriate statistical descriptors, and the distribution of data is skewed, then the mean and standard deviation should also be provided.

44) The incidence[j] of events meeting the case definition should be presented and clearly identified as such in the text.

45) Any publication of AEFI data should include a detailed description of the methods used for data collection and analysis. It is essential to specify

- type of surveillance system (e.g., passive surveillance, active surveillance);
- characteristics of the surveillance systems (e.g., population served, mode of report solicitation);
- instrument for data collection (e.g., report form, standardized questionnaire);
- search strategy in surveillance databases;
- comparator group(s), if used for analysis;
- the data analysis plan per protocol, and the statistical plan; and any amendments to these sections of the protocol added during the study;
- whether the day of immunization was considered "day one" or "day zero" in the analysis;
- whether the date/time of onset[b] and/or first observation[c] and/or diagnosis[d], and the end of episode[e] and/or final outcome[f] were used for analysis; and
- reference of the case definition used (Brighton Collaboration or other) should be mentioned in the abstract or method section of a publication[k].

Notes for guidelines

[a] If the reporting center is different from the vaccinating center, appropriate and timely communication of the adverse event should occur.

[b] The date and/or time of onset is defined as the time post immunization, when the first sign or symptom indicative for the AEFI occurred. This may only be possible to determine in retrospect.

[c] The date and/or time of first observation of the first sign or symptom indicative for the AEFI can be used, if date/time of onset is not known.

[d] The date of diagnosis of an episode is the day post immunization when the event met the case definition at any level.

[e] The end of an episode is defined as the time the event no longer meets the case definition.

[f] An AEFI not resolved at the time of reporting or evaluation may be followed up as clinically necessary, and additional reporting should be encouraged in order to describe progress until the final outcome. "Persistence of event" refers to events continuing to meet the case definition beyond the last time of follow-up. "Sequelae" are long-term clinical consequences resulting from the event.

[g] If the lowest level of a case definition is not met, it should be ruled out that any of the higher levels of diagnostic certainty are met and the event should be classified in category 4 or 5.

[h] If the evidence available for an event is insufficient to permit classification by any level of diagnostic certainty (e.g. because of missing information), such an event should be categorized as "reported [*AEFI*] with insufficient evidence to meet a case definition". Notations should be made as to what evidence is missing.

[i] If there is adequate evidence that an event does not meet a case definition, such an event should be rejected and should be reported as "Not a case of [*AEFI*]". Such evidence is considered adequate, if an exclusion criterion is met, or investigation reveals a negative finding of a necessary criterion (necessary condition) for diagnosis.

[j] e.g., cumulative incidence rate: 10 cases of a given AEFI among 1 million doses administered; or incidence rates: 3 cases of a given AEFI on day 1, 2 cases on day 2, 10 cases on day 3 following immunization, or 0 cases after the first dose, 1 case after the second dose, 10 cases after the third dose.

[k] Use of this or AEFI-specific documents developed by the Brighton Collaboration should be referenced by referring to the link on the Brighton Collaboration website (https://brightoncollaboration.org/public).

Acknowledgements

The authors are grateful for the support and helpful comments from members of the Brighton Collaboration Steering Committee during the time of the development of this document, who are not already included as authors (Elisabeth Loupi, Miles Braun, Brigitte Keller Stanislawski), and the participants in the Reference Group (Raymundo Azevedo, Rolando Ochoa Azze, Michael Blum, Dean Blumberg, Thomas Cherian, Bakary Drammeh, Philippe Duclos, Delia A. Enria, Birgitta Evengard, Farhad Handjani, John Hansen, Marcy Connell Jones, Daniele Kohl, Jerry Labadie, Glenda Lawrence, David G. McIntosh, Suzanne Menard, Tony Nelson, Suchitra Nimmannitya, James Oleske, Gabriele Poerschke, Keith Powell, Edward Rothstein, Synne Sandbu, Ines Schoendorf, Françoise Sillan, Russell Steele, Gillian A. Stoltman, Amina Tebaa, Eveline Toth, Alberto Tozzi, John Treanor, Patricia Vermeer, Beverly Warden), and harmonization work by Jane Gidudu and Michael Büttcher.

Finally, we would like to thank the members of the WHO/CIOMS Working Group on Vaccine Pharmacovigilance (http://www.cioms.ch/activities/frame_vaccpharma.htm) for the review of, constructive comments on, and endorsement of this document.

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Sample Report Form for Adverse Events Following Immunization (for surveillance systems)

ADVERSE EVENT REPORT

Patient and reporter identity is confidential. Complete the form to the best of your abilities.

Required fields are marked with an asterisk (*) and printed in bold. Please indicate units used (for fever, for length, for lab test results, etc.).

Should you require more space than provided to report all relevant data, please use additional pages and refer to the respective questions on the form.

A. Source of Information/ Reporter

For internal use only:
Report no.: _____

1) Date of this report*: ___/___/___ (DD/MM/YYYY) **2) Report type*:** ☐Initial ☐Follow-up

3) First name*: _____ Middle initial: _____ **Last name*:** _____

4) Phone: +____ (_____)_____Fax: +____ (_____)_____

5) Address*: _____ **Street*:** _____

Country*: _____ State: _____ **Postcode/ ZIP*:** _____**City*:** _____ email:_____

6) Relation to patient: ☐Immunizer (physician/nurse) ☐Patient/ Family member (indicate relationship) ☐Manufacturer ☐Other(specify)_____

B. Vaccinee/Control

7) Patient initials[1] (first name/ last name) ___ /____

8) Birth date*: ___/___/___ (DD/MM/YYYY) **9) Sex*:** ☐M ☐F ☐Unknown 10) Infants: Gestational age:_____ birth weight:_____

11) Was the patient seen by a physician for the adverse event reported on this form? ☐Yes ☐No ☐Unknown

12) Pre-vaccination signs or symptoms on day of vaccination (e.g. cold, fever): ☐Yes ☐No ☐Unknown If YES, please describe:

_____

_____

13) Any medication prior to, during, and after the adverse event including prescription and non-prescription medication (e.g., herbal or homeopathic medication) as well as medication with long half-life or long-term effect (e.g., immunoglobulins, blood transfusion, immunosuppressants, oral or intravenous corticosteroids), that could affect the evaluation of an AEFI, but other than treatment given for the AEFI. ☐Yes ☐No ☐Unknown
If YES, please specify:

_____

_____

14) Medical history: List any prior hospitalizations and diagnoses, or other significant medical history of any medical or psychological disorders or serious injuries including treatment (e.g., pregnant, allergies, seizures, events similar to or related to the AEFI)

_____

_____

15) Did the patient experience any adverse events other than the current one to previous doses of the same vaccine? ☐Yes ☐No ☐Unknown
If YES, describe in detail including dates of occurrence:

_____

_____

16) Relevant family history? ☐Yes ☐No ☐Unknown If yes, please specify:

_____

_____

[1] While the name or initials of the patient would be highly valuable for follow-up, it is recognized that this information is often subject to the provisions of the respective national regulatory agency's privacy act or the country-specific data protection law.

C. Details of the Immunization

17) Please provide available details of the patient's vaccination history*.

Date (DD/MM/YYYY)	Time (hh:mm)	Vaccine	Manufacturer	Lot number	Lot of diluent	Multi-dose package[1]	Expir. date (DD/MM/YYYY)	Dose[2]	No. of dose in series[3]	Route[4]	Anatomical site[5]	Device[6]	Source of information[7]

[1] e.g., 50 ml vial; [2] e.g., 1 ml; [3] against same disease; [4] route of administration (e.g., i.m., s.c.); [5] e.g. left arm, deltoid area; [6] e.g., syringe; needle: 4 cm, 18"; [7] e.g., medical record, history

D. The Adverse Event

18) Final diagnosis of AE: _____ 19) Date and time of diagnosis: ___/___/___ (DD/MM/YYYY)

20) Date and time of onset (time of first sign or symptom indicative for the primary AEFI)*: ___/___/___ (DD/MM/YYYY)

21) Describe the sequence of events including times, dates, symptoms, signs and test results supporting diagnosis*:

_____
_____
_____
_____
_____
_____
_____
_____

22) List any treatments given for the AEFI including times and dates:

_____
_____

23) Has patient's condition returned to pre-vaccination health status? ☐Yes ☐No ☐Unknown
If YES, indicate when pre-vaccination heath status was reached: ___/___/___ (DD/MM/YYYY)
If NO, indicate whether the patient has any persistent signs or symptoms, residual disability or sequelae, and what has happened to date:

_____
_____

24) Was the patient re-vaccinated (i.e., were further doses applied?) ☐Yes ☐No ☐Unknown
If YES, describe the outcome

_____
_____

This report from the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with WHO covers the activities and outputs of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance (2005-2010).

This working group brought together experts from both industrialized and emerging countries representing regulatory agencies, vaccine industry, national and international public health bodies including WHO and CIOMS, academia and clinical care, contributing from their different perspectives.

The working group's report covers general terms and definitions for vaccine safety and discusses the application of such harmonized tools in vaccine safety surveillance and studies. As well, the report highlights case definitions for adverse events typically reported for vaccines.

The report is addressed to those engaged in vaccine safety data collection and evaluation, and will also make a useful reading for others who want to familiarise themselves with vaccine safety terminology.

ISBN 978-92-9036-083-4